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Exanthem Subitum-Associated Encephalitis: Nationwide Survey in Japan

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We sought to clarify clinical features of exanthem subitum associated-encephalitis/encephalopathy, generally caused by primary human herpesvirus-6 infection in Japan. A two-part questionnaire was sent to hospitals between January 2003-December 2004. Of 3357 questionnaires, 2357 (70.2%) were returned, and 2293 (68.3%) were eligible for analysis. Eighty-six cases of exanthem subitum-associated encephalitis/encephalopathy were reported. Seventy-seven (89.5%) of 86 patients were diagnosed with human herpesvirus-6 infection by virologic examination. Although 41 (50.6%) of 81 patients had no sequelae, 38 (46.9%) had neurologic sequelae. Moreover, two fatal cases (2.5%) were reported. Pleocytosis was evident in only 4 (7.5%) of 53 patients, and cerebrospinal fluid protein levels were within normal range (23.4 ± 14.6 mg/dL S.D.) in all patients. Human herpesvirus-6 DNA was detected in 21 (53.8%) of 39 patients. Abnormal computed tomography findings were a predictor of neurologic sequelae (P = 0.0097). As a consequence of this survey, we estimate that 61.9 cases of exanthem subitum-associated encephalitis occur every year. The disease prognosis was unexpectedly poor. **© 2009 by Elsevier Inc. All rights reserved.**

Yoshikawa T, Ohashi M, Miyake F, Fujita A, Usui C, Sugata K, Suga S, Hashimoto S, Asano Y. Exanthem subitum-associated encephalitis: Nationwide survey in Japan. Pediatr Neurol 2009;41:353-358.

Introduction

Primary human herpesvirus-6 infection can cause exanthem subitum in infants and young children [1]. Although the disease is generally a benign, febrile illness with a self-limiting clinical course [2], several severe manifestations, particularly in the central nervous system, can occur [3-13]. Exanthem subitum is associated with febrile seizures [14]. Moreover, we found that the incidence of severe forms of febrile seizures, e.g., hemiconvulsions, prolonged seizures, and repeated seizures, was high in cases of exanthem subitum-associated febrile seizures [15]. After human herpesvirus-6 was identified as an etiologic agent of exanthem subitum, human herpesvirus-6 encephalitis/encephalopathy was reported by several investigators [3-13]. Some studies reported on patients who recovered completely, whereas others manifested severe neurologic sequelae, including several cases with fatal outcomes [4,8,16]. Human herpesvirus-6 DNA was detected in the cerebrospinal fluid of several patients via polymerase chain reaction [5,6], suggesting direct viral invasion of the central nervous system. Saito et al. [17] detected viral antigens and DNA in postmortem brain tissues obtained from AIDS patients, which supports the concept of direct invasion of the virus into the central nervous system. Moreover, it was suggested that human herpesvirus-6 can infect not only neurologic cell lines [18-20] but also fetal astrocytes [21], and can alter cytokine synthesis in infected cells [22]. Thus, human herpesvirus-6 is recognized as a neuro-pathogen. Although a recent study from the United Kingdom indicated that human herpesvirus-6 and human herpesvirus-7 are associated with encephalitis or severe forms of febrile seizure [23], details of the clinical features and frequency of human herpesvirus-6 encephalitis/encephalopathy remain unclear. Therefore, we performed a nationwide survey to determine the frequency and clinical features of exanthem subitum-associated encephalitis/encephalopathy in Japan.

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This work was presented in part at the 45th Annual Infectious Diseases Society of America, San Diego, California, October 4-7, 2007.

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Received February 7, 2009; accepted May 11, 2009.

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doi:10.1016/j.pediatrneurol.2009.05.012 • 0887-8994/09/$—see front matter

Materials and Methods

A two-part questionnaire sought to determine the number of cases and clinical features of the disease over a 2-year period, between January 2003-December 2004. The first part included six questions. The first question asked if the hospital had hospitalized cases of exanthem subitum-associated encephalitis/encephalopathy, because all patients with the disease are thought to be admitted to hospitals for intensive treatment. Exanthem subitum-associated encephalitis/encephalopathy was defined as exanthem subitum in patients with stupor or convulsion. To exclude exanthem subitum patients with severe forms of febrile convulsion, abnormal findings of radiologic examinations were required for diagnoses of patients with only convulsions to indicate exanthem subitum-associated encephalitis/encephalopathy. If a hospital reported a case of exanthem subitum-associated encephalitis, five questions were asked: (1) age of patients, (2) sex of patients, (3) presence or absence of human herpesvirus-6 virologic examinations and the examination methods used (significant increase in human herpesvirus-6 IgG antibodies, positive human herpesvirus-6 immunoglobulin M, positive human herpesvirus-6 DNA in serum, and human herpesvirus-6 isolation), (4) detection of human herpesvirus-6 DNA in cerebrospinal fluid via polymerase chain reaction, and (5) the patients' prognosis. The second part of the questionnaire was subsequently sent to hospitals that reported cases of exanthem subitum-associated encephalitis/encephalopathy, and focused on clinical features such as (1) a febrile period, (2) time of skin-rash appearance, (3) onset of neurologic signs, (4) cerebrospinal fluid findings, including the presence or absence of human herpesvirus-6 DNA, (5) electroencephalogram findings, (6) radiologic findings, including computed tomography and magnetic resonance images, (7) treatments, including antiviral drugs, steroids, and gamma-globulins, and (8) the patients' prognosis.

In March 2005, the first questionnaire was mailed to the chiefs of pediatric departments in the 3357 hospitals with pediatric wards throughout Japan. A second mailing was sent to nonresponders in August 2005 to increase survey reliability. In December 2005, the second part of the questionnaire was sent to hospitals that reported patients with exanthem subitum-associated encephalitis/encephalopathy in the first questionnaire.

Data analysis was performed by members of our laboratory. An association between seven clinical factors, including sex, age, onset of neurologic signs, presence of human herpesvirus-6 DNA in cerebrospinal fluid, abnormal electroencephalogram findings, abnormal computed tomography findings, and abnormal magnetic resonance imaging findings and neurologic sequelae, were examined via χ^2 test. The statistical analysis was performed using StatView software, version J-5.0 (distributed by HULINKS, Inc.). The protocol of this study was approved by the Review Board of Fujita Health University.

Results

Results of First Questionnaire

Of 3357 questionnaires sent to hospitals, 2357 (70.2%) were returned. Fifty-seven (2.4%) pediatric wards were closed, and seven questionnaires (0.3%) were returned without any information, leaving 2293 (68.3%) eligible for analysis. Eighty-six patients (45 male [52.3%] and 41 female ([47.7%]) with exanthem subitum-associated encephalitis/encephalopathy were reported at 61 hospitals (2.7%), and no patients with encephalitis/encephalopathy were reported at the remaining 2232 hospitals (97.3%). Seventy-seven (89.5%) of 86 patients were diagnosed with human herpesvirus-6 infection according to virologic examinations, e.g., viral isolation (1 patient), serologic assay (53 patients), and plasma polymerase chain reaction (34 patients). Eleven patients were diagnosed with human herpesvirus-6 infection using two different virologic examinations. Only nine patients (10.5%) were diagnosed with exanthem subitum according to typical clinical features of the illness. The mean age of patients was 14.0 ± 8.8 months S.D. The youngest patients were 3 months old, and a peak in patient numbers was evident at age 10 months. Eight patients were older than 24 months. A prognosis was available for 81 (94.2%) of 86 patients. Although 41 (50.6%) of the 81 patients manifested no sequelae, 38 (46.9%) of 81 patients manifested neurologic sequelae. Moreover, two fatal cases (2.5%) were reported. Details of neurologic sequelae were examined in the second questionnaire.

Results of Second Questionnaire

To collect more precise information, a second questionnaire was sent to hospitals that had reported patients with exanthem subitum-associated encephalitis/encephalopathy in the first questionnaire. Data for the second questionnaire were collected regarding 60 of the 86 patients, and several analyses were performed on the data gathered from these 60 patients. To predict the pathogenesis of the exanthem subitum-associated central nervous system manifestations, a time correlation between the onset of neurologic signs and the appearance of a skin rash was evaluated in 56 patients, because data on disease onset were not available for four patients. We defined the day when a skin rash appeared as day zero. Neurologic signs occurred before and after the appearance of a skin rash in 37 (66.1%) and 11 (19.6%) patients, respectively. One patient (1.8%) manifested neurologic signs when a skin rash appeared. No skin rashes were evident in seven patients (12.5%), diagnosed according to virologic examinations. Forty-three (71.7%) of the 60 patients manifested stupor and convulsion, whereas the remaining 17 patients (28.3%) manifested only convulsions during the observation period. However, abnormal magnetic resonance imaging findings were evident in these 17 patients.

Table 1. Summary of abnormal findings in radiologic examinations

Examination	Patients With Abnormal Findings/Patients Examined	Abnormal Findings	Number of Patients
CT	21/54 (38.9%)	Brain edema	14
		Low density area	
		Frontal and temporal lobe	3
		Left hemisphere	1
		Bilateral striatum region	1
MRI	34/50 (65.4%)	Hyperintense on diffusion image*	21
		Brain atrophy†	10
		Hyperintense on T_2-weighted image	9
		Brain edema	5
		Subdural effusion	3
		Hyperintense on FLAIR	2
		Hyperintense on T_1-weighted image	1
		Hypointense on T_1-weighted image	1

* Without corresponding apparent diffusion coefficient result.
† Brain atrophy was evident late in time course (later than 10 days after onset of illness) in 9 of 10 patients.

Abbreviations:
CT = Computed tomography
FLAIR = Fluid-attenuated inversion recovery
MRI = Magnetic resonance imaging

Cerebrospinal fluid findings were available for 53 patients. Pleocytosis (20 cells/μL, 15 cells/μL, 11 cells/μL, and 51 cells/μL) was evident in only 4 (7.5%) of 53 patients, and the remaining 49 patients (92.5%) demonstrated normal cell counts. Cerebrospinal fluid protein levels were within normal range (23.4 $\pm$ 14.6 mg/dL) in all patients. The presence of human herpesvirus-6 DNA in cerebrospinal fluid was examined in 39 (65.0%) of 60 patients via polymerase chain reaction. Human herpesvirus-6 DNA was detected in 21 (53.8%) of those 39 patients. Electroencephalogram findings in the acute phase of the illness (within 10 days after onset of illness) were available for 55 patients. Abnormal findings (31 patients with high-voltage slow waves, 4 patients with spikes, 7 patients with other findings, and 14 patients without abnormal findings) were evident in 42 (76.4 %) of 55 patients. Computed tomography and magnetic resonance imaging of the brain were performed in 54 and 50 patients, respectively. The radiologic findings are summarized in Table 1. Computed tomography was performed 3.0 $\pm$ 2.1 days after the onset of illness. Abnormal findings (14 patients with brain edema, five patients with low-density areas, and two patients with other findings) were evident in 21 (38.9%) of 54 patients. Magnetic resonance imaging was performed 8.7 $\pm$ 5.5 days after the onset of illness, and 34 (68.0%) of 50 patients manifested abnormal findings, including 21 patients with hyperintensity on a diffusion-weighted image (without the corresponding apparent diffusion coefficient result).

Antiviral drugs were administered to 31 (51.7%) of 60 patients. Acyclovir was used in 28 patients, ganciclovir in one patient, and a combination of both drugs in two patients. Thirty-three (55.0%) of 60 patients received steroid treatments, including three who received steroid pulse therapy. Immune globulin was administered to 19 (31.7%) of 60 patients, including seven patients with high-dose γ-globulin treatment.

Neurologic sequelae were evident in 32 (53.3%) of 60 patients. As shown in Table 2, cases of severe neurologic sequelae were reported, including nine patients with spastic quadriplegia, eight patients with mental retardation, and seven patients with hemiplegia. Two fatal cases were reported from two different hospitals.

Association Between Clinical Factors and Neurologic Sequelae or a Fatal Clinical Course

As described in Table 3, an association between six clinical factors and neurologic sequelae or a fatal clinical course was evaluated. No statistical association was evident between sex, age, or onset of neurologic signs and neurologic sequelae. Although 9 (42.9%) of 21 patients with positive human herpesvirus-6 DNA in cerebrospinal fluid manifested neurologic sequelae, 13 (72.2%) of 18 patients without human herpesvirus-6 DNA in their cerebrospinal fluid manifested neurologic sequelae. Thus, patients with human herpesvirus-6 DNA in their cerebrospinal fluid exhibited less frequent neurologic

Table 2. Summary of neurological sequelae

Neurologic Sequelae	Number of Patients
Spastic quadriplegia	9
Psychomotor retardation	8
Hemiplegia	7
Motor retardation	3
Epilepsy	2
Speech disturbance	2
Facial nerve paralysis	1

Table 3. Associations between six clinical factors and neurologic sequelae or fatal clinical course

Factors (n)	Neurological Sequelae (Yes/No)	*P* Value
Sex (60)		
Male	16/14	0.6023
Female	18/12	
Age (60)		
Infant	24/15	0.2994
Older than 12 months	10/11	
Onset of neurologic signs (49)		
Febrile period	21/16	0.1584
Exanthematous period	4/8	
HHV-6 DNA in CSF (39)		
Positive	9/12	0.0652
Negative	13/5	
Abnormal findings in CT (54)		
Yes	17/4	0.0097
No	15/18	
Abnormal findings in MRI (52)		
Yes	24/12	0.1201
No	7/9	

Abbreviations:
CSF = Cerebrospinal fluid
CT = Computed tomography
HHV-6 = Human herpesvirus-6
MRI = Magnetic resonance imaging

sequelae, although no statistical association was observed ($P = 0.0652$). Meanwhile, 17 (81.0%) of 21 patients with abnormal computed tomography findings manifested neurologic sequelae, whereas 15 (45.5%) of 33 patients without abnormal findings manifested sequelae, and the frequency of neurologic sequelae was significantly higher in patients with abnormal computed tomography findings than in those without abnormal findings ($P = 0.0097$). No statistical association was observed between abnormal electroencephalogram ($P = 0.1893$) or magnetic resonance imaging ($P = 0.1201$) finding and neurologic sequelae.

Discussion

After sending questionnaires to 3300 hospitals with pediatric wards, 2293 (69.5%) hospitals responded, and 86 patients with exanthem subitum-associated encephalitis were found during the 2-year observation period. Thus, the annual number of cases of this disease is estimated at 61.9 patients/year, under the assumption that the response from hospitals was independent of the frequency of patients. Because the response rate of the questionnaire was 70%, the assumption needs to be validated. Hashimoto et al. [24] compared the mean numbers of patients with intractable disease who were financially subsidized for treatment from responding departments with those from nonresponding departments. The ratio of the former to the latter was 1.0:1.1. This value suggests that the assumption might be sufficiently valid for nationwide epidemiologic surveys of intractable diseases in Japan.

Although this survey was designed to identify patients based on a clinical diagnosis of exanthem subitum, almost 90% of patients were diagnosed via virologic examinations, including seven patients (12.5%) with an atypical clinical course of exanthem subitum (without skin rash). It is possible that other etiologic agents such as human herpesvirus-7 [25,26] or enterovirus, which are considered agents for exanthem subitum-like illnesses, may have been involved in the 10% of patients without virologic examinations. Therefore, the annual number of patients with exanthem subitum-associated encephalitis/encephalopathy estimated in this survey may be slightly different from the annual number of patients with human herpesvirus-6 encephalitis/encephalopathy. To elucidate the precise frequency of the disease, future nationwide surveys for human herpesvirus-6 encephalitis/encephalopathy should be based on virologic examinations. In contrast to influenza virus infection, the annual number of patients with exanthem subitum is stable every year. Therefore, we think that almost 60 new cases of exanthem subitum-associated encephalitis/encephalopathy occur every year in Japan. At present, annual birthrate is almost 1,100,000/year in Japan. Moreover, according to the results of our epidemiologic study [27], most children are susceptible to human herpesvirus-6 infection. Therefore, if we hypothesize that most infants (approximately 1,100,000) contract human herpesvirus-6 infection every year, the incidence of exanthem subitum-associated encephalitis/encephalopathy would be estimated at 5.5 cases/100,000 exanthem subitum cases.

The most important finding in this survey is that the disease prognosis was unexpectedly poor. Nearly half of the patients manifested neurologic sequelae after exanthem subitum-associated encephalitis/encephalopathy. Furthermore, many patients manifested severe neurologic sequelae (Table 2), and an additional two cases were fatal. One patient with exanthem subitum-associated encephalitis [28] and a patient with human herpesvirus-6 encephalitis [29] manifested hemiplegia as neurologic sequelae. In addition to hemiplegia, several patients with spastic quadriplegia were also reported in our survey. Thus, paralysis is likely to be among the common and severe neurologic sequelae of exanthem subitum-associated encephalitis/encephalopathy. Although fatal cases of human herpesvirus-6 encephalitis were reported mainly in immunocompromised adult patients [30-33], three fatal cases of human herpesvirus-6 encephalitis in immunocompetent children have been reported to date [4,8,16]. Details on the two fatal cases reported in this survey are not clear. To clarify the pathogenesis of fatal cases, and therefore improve disease prognosis, a more in-depth analysis of patients with fatal exanthem subitum-associated encephalitis/encephalopathy is needed.

Predicting patient prognoses is important for clinicians. Neither patients' sex nor age was associated with the occurrence of neurologic sequelae. Insofar as it was demonstrated that human herpesvirus-6 viremia occurs during the febrile period of exanthem subitum, and that the virus isolation rate rapidly decreases after fever subsides [34],

the pathogenesis of human herpesvirus-6 encephalitis/encephalopathy may be different between patients with febrile-period onset and those with exanthematous-period onset. However, the onset of neurologic signs did not correlate with the occurrence of sequelae. The frequency of neurologic sequelae was higher in patients with abnormal computed tomography findings than in those with normal findings ($P = 0.0097$), suggesting that computed tomography is a useful procedure for predicting patients' prognoses. Magnetic resonance imaging is considered more sensitive than computed tomography for the detection of abnormal radiologic findings. However, magnetic resonance imaging did not predict the occurrence of neurologic sequelae, and abnormal findings were evident in 12 of 21 patients without neurologic sequelae, probably because of excess sensitivity.

Although specific findings of exanthem subitum-associated encephalitis/encephalopathy could be useful for patient management, no characteristic findings have been demonstrated to date. Examination of cerebrospinal fluid is useful in diagnosing central nervous system infections. In contrast to herpes simplex encephalitis, most patients exhibited normal cerebrospinal fluid in this survey. Detecting viral DNA in cerebrospinal fluid is important for determining the etiologic agent of the disease, and human herpesvirus-6 DNA was detected in 53.8% of patients in this survey. However, because polymerase chain reaction protocols and sensitivities are not standardized, further studies using a standardized polymerase chain reaction protocol are necessary to determine the detection rate of human herpesvirus-6 DNA in these patients. Recently, it was demonstrated that diffusion-weighted magnetic resonance imaging (without the corresponding apparent diffusion coefficient result) or fluid-attenuated inversion recovery magnetic resonance imaging is useful in the early detection of abnormal findings in encephalitis patients [35]. In this survey, abnormal findings in diffusion-weighted magnetic resonance imaging were reported for many patients, but these observations varied, without any specific findings. Furthermore, the mean time for performing magnetic resonance imaging was 8.7 days after onset of illness, which suggests that magnetic resonance imaging may be difficult to perform in the acute phase of the disease. To evaluate the reliability of radiologic examinations for detecting the characteristic findings of the disease, it is necessary to define a protocol for radiologic examinations, and to analyze a large number of cases prospectively. Moreover, details of radiologic findings should be examined in future surveys, to identify the characteristics of exanthem subitum-associated encephalitis/encephalopathy.

Although this study provides important information about exanthem subitum-associated encephalitis/encephalopathy (in particular, the unexpectedly high incidence of severe neurologic sequelae), it has several limitations because it was a questionnaire-based epidemiologic study. Although a severe case of encephalitis is easy to diagnose in exanthem subitum-associated encephalitis/encephalopathy, it may be difficult to distinguish between mild encephalitis/encephalopathy and atypical febrile seizures in a case with mild signs. Therefore, different thresholds for the diagnosis of mild exanthem subitum-associated encephalitis/encephalopathy among pediatricians might affect case reports. Moreover, the possibility of bias at the responding hospitals cannot be completely ruled out. To solve these problems, a future prospective study following exanthem subitum-associated encephalitis/encephalopathy within a small area (e.g., Aichi Prefecture) is necessary.

This work was supported in part by a Grant-in-Aid for the 21st Century Centers of Excellence Program of Medicine and by the Open Research Center, both at Fujita Health University, and by the Ministry of Education, Culture, Sports, Science, and Technology of Japan. The authors have no commercial or other associations that might pose a conflict of interest.

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Parkinsonism and Related Disorders 15 (2009) 15–19

Parkinsonism & Related Disorders

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Correlation between depressive symptoms and nocturnal disturbances in Japanese patients with Parkinson's disease

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Received 10 November 2007; accepted 4 February 2008

Abstract

Depression and nocturnal disturbances are frequent in patients with Parkinson's disease (PD). The aim of this study was to determine the correlation between depressive symptoms and nocturnal disturbances in patients with PD in Japan. The subjects of this multi-center cross-sectional study were 188 patients with PD and 144 age-matched controls who were assessed for nocturnal disturbances by the Parkinson's disease sleep scale (PDSS) and for depressive symptoms by Zung Self-Rating Depression Scale (SDS). Depressive symptoms (SDS score of $\geq$40) were identified in 122 patients (64.9%). The SDS was significantly higher in PD patients than control subjects. The stepwise regression model identified PDSS ($p < 0.001$) and Unified Parkinson's Disease Rating Scale I (mental state) ($p = 0.002$) as significant determinants of SDS. Stepwise regression analysis identified item 15 (daytime sleepiness) ($p = 0.002$), item 13 (early morning tremor) ($p = 0.008$), item 12 (nocturnal dystonia) ($p = 0.015$), and item 3 (sleep maintenance insomnia) ($p = 0.026$) as significant predictors of SDS. Our results indicated that depressive symptoms in PD correlate significantly with nocturnal disturbances, and that daytime sleepiness, dystonia, tremor and sleep fragmentation are the most common nocturnal disturbances in depressed patients with PD.
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Keywords: Parkinson's disease; Depression; Zung Self-Rating Depression Scale (SDS); Parkinson's disease sleep scale (PDSS); Nocturnal disturbances

1. Introduction

Non-motor symptoms such as cognitive dysfunction, psychiatric symptoms, and sleep disorders have attracted attention recently, in addition to motor symptoms, in Parkinson's disease (PD). In a community-based study, two-thirds of the patients with PD reported sleep disorders [1]; however, the etiology is still controversial. About 40% of PD patients have depression [2], which also involves sleep disorders [3] and is associated with impairment of activities of daily living [4]. Chaudhuri and Martinez-Martin [5] found a significant correlation between sleep disturbances and depression using the Parkinson's disease sleep scale (PDSS) [6], useful for multifactorial nocturnal problems. Using PDSS, other studies reported that sleep disturbances were associated with disease severity, daytime sleepiness [7], and impairment of activities of daily living [8]. Dhawan et al. [9] reported that untreated

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1353-8020/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.parkreldis.2008.02.002

PD had many nocturnal problems, such as nocturia, nighttime cramps, dystonia, tremor, and daytime sleepiness in PDSS sub-items, suggesting that sleep disorders in PD are more likely to be related to the underlying dopaminergic deficit rather than the effect of dopaminergic treatment. On the other hand, severer changes in monoamines, such as dopamine, serotonin and noradrenalin are reported in the brain of depressed patients than non-depressed patients in PD [2, 10], and it has been reported that depression develops prior to the motor symptoms in PD patients [11]. Therefore, sleep disruption caused by depression may reflect the pathological course of the disease itself in PD.

Although we reported previously that the depressive state is a significant determinant of sleep disorders in PD [12], the specific nocturnal disturbances related to depressive symptoms remain elusive.

To determine the true status of nocturnal disturbances associated with depressive symptoms and the frequency of depressive state in Japanese patients with PD, we conducted the present survey using the PDSS [6] and Zung Self-Rating Depression Scale (SDS) [13] at multiple facilities. This study was a part of an epidemiological study on non-motor symptoms in PD [12].

2. Subjects and methods

A consecutive series of 251 patients with idiopathic PD consulted the participating eight medical university hospitals in the Kanto area of Japan during the period between April and December 2005. The current population of Kanto area is, approximately, 43 million (34.3% of all Japan). The area is called the metropolitan area and includes the city of Tokyo. Semi-structured, questionnaire-based interviews were conducted among these 251 patients. Of the 251 patients, 188 (85 men and 103 women) were assessed for sleep problems and depressed symptoms. Thirty-six gave incomplete answers in the questionnaire, 1 was bedridden, 1 was less than 40 years of age and had juvenile PD, and 25 had dementia. The cognitive function and dementia were evaluated by the Mini Mental State Examination and a score of less than 24 points was regarded as indicative of dementia. The mean age of patients was 66.4 ± 8.7 years ($\pm$ standard deviation) and the disease duration was 6.9 ± 5.3 years. For comparison, we studied 144 age-matched healthy control subjects (65.1 ± 6.8 years, 64 men and 80 women) in the Kanto area of Japan. The control subjects had no history of ischemic heart disease, painful joint disease, neurologic disease (include stroke), chronic obstructive airway disease and psychiatric disease and taking no hypnotic drugs and antidepressants.

The diagnosis of PD was based on the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria [14]. In other words, PD patients were defined as having bradykinesia and at least one of the following three symptoms: resting tremor, muscular rigidity, and/or postural instability. Parkinsonism, such as that induced by chemical or vascular insults, was excluded from disease history and imaging diagnosis. Furthermore, all patients were assessed by a neurologist and confirmed to be free of progressive supranuclear palsy, multiple system atrophy, corticobasal degeneration and other forms of atypical parkinsonism.

PD patients were evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS), Hoehn and Yahr (H&Y) stage for evaluation of disease severity. The mean H&Y stage and UPDRS of all PD patients were 2.5 ± 0.8 and 32.9 ± 18.1, respectively.

With regard to medications, 148 patients had taken levodopa with decarboxylase inhibitor (levodopa/DCI), with a mean dosage of 366.9 ± 157.7 mg/day, while 130 patients had taken dopamine agonists (DA), with a mean equivalent levodopa dose of 240.5 ± 161.1 mg/day [15].

Symptoms of depression were assessed using the SDS [13]. The SDS Japanese version has been well validated [16]. The SDS has been used widely in various patient groups and in healthy subjects, providing considerable validation data as well as a large number of comparison groups [17]. The SDS scale has 20 items selected to represent the various symptoms of clinically significant depression. Each item is rated 1–4, with higher scores representing greater symptom severity. The presence of depressive symptom was defined as SDS raw score of ≥ 40, since this cut-off point was recommended to distinguish depressed patients from controls [18].

All patients were evaluated for sleep disturbances using the PDSS-Japanese version [19]. The PDSS, which is a visual analog scale type questionnaire, consists of 15 items on sleep disorders and nocturnal problems associated with PD (see Appendix 1) [6]. Sub-items of PDSS address the following: overall quality of night's sleep (item 1); sleep onset and maintenance insomnia (items 2 and 3); nocturnal restlessness (items 4 and 5); nocturnal psychosis (items 6 and 7); nocturia (items 8 and 9); nocturnal motor symptoms (items 10–13); sleep refreshment (item 14); daytime dozing (item 15). Scores for a given individual item range from 0 to 10. Ten represents the best, 0 represents the worst score. The maximum total score for PDSS is 150 (patient is free of symptoms associated sleep disorders).

The study was approved by the institutional review boards appropriate for each investigator and all study participants gave written informed consent.

3. Statistical analysis

The Mann–Whitney U test was used for continuous data and the chi-square test was used for categorical variables. Kruskal Wallis test was used to test differences in sub-items of PDSS and PDSS total score between PD (depressed and non-depressed patients) and controls. The Spearman's correlation was calculated to compare the SDS and the PDSS total score in PD patients. A stepwise regression model was used to identify the determinants of SDS in PD patients that included age, gender, disease duration, PDSS, H&Y stage, UPDRS I (mental state), UPDRS II (activities of daily living), UPDRS III (motor performance), UPDRS IV (complications of treatment), use of any DA, and use of levodopa/DCI. Subsequently, stepwise regression analysis was applied to determine the important PDSS sub-items for SDS. Significance of differences was defined as two-tailed $p < 0.05$. SPSS II Windows Ver 11.0 (SPSS Japan Inc.) was used for statistical analyses. All data are expressed as mean $\pm$ standard deviation.

4. Results

The SDS score was higher in PD patients (43.4 ± 9.6) than in controls (35.4 ± 8.2) ($p < 0.001$). Of the 188 PD patients, 122 (64.9%) had depressive symptoms. Table 1 shows the clinical characteristics of depressed and non-depressed patients with PD. There were no differences in age, gender differences, and disease duration. Depressed patients had significantly higher scores of H&Y stages and UPDRS I–IV, and higher dose of levodopa/DCI compared with non-depressed patients. Significant differences in PDSS total scores and PDSS sub-items except PDSS items 2 and 11 were seen among depressed patients, non-depressed patients, and controls (Table 2, Fig. 1). However, there was no difference in PDSS total scores and PDSS sub-items except PDSS item 13 between controls and non-depressed patients.

The PDSS total score correlated significantly with the SDS in PD patients ($r = -0.41$, $p < 0.001$, Fig. 2). In PD patients, stepwise regression model with SDS as the dependent variable

Table 1
Clinical characteristics of depressed PD patients, non-depressed PD patients and control subjects

	Non-depressed PD	Depressed PD	Total PD	p Value
Number	66	122	188	
Men/women	36/30	49/73	85/103	0.059[a]
Age	66.8 ± 9.7	66.2 ± 8.2	66.4 ± 8.7	0.473
Disease duration	6.0 ± 5.1	7.4 ± 5.3	6.9 ± 5.3	0.056
H&Y stage	2.3 ± 0.7	2.6 ± 0.8	2.5 ± 0.8	0.014
UPDRS total score	27.0 ± 14.7	36.0 ± 19.1	32.9 ± 18.1	0.001
UPDRS I	0.6 ± 0.9	1.4 ± 1.9	1.1 ± 1.7	<0.001
UPDRS II	7.8 ± 5.3	10.3 ± 6.6	9.4 ± 6.3	0.010
UPDRS III	17.3 ± 9.7	21.8 ± 11.7	20.2 ± 11.2	0.010
UPDRS IV	1.3 ± 1.6	2.5 ± 3.4	2.1 ± 3.0	0.045
Levodopa/DCI (mg/day)	240.9 ± 193.5	314.8 ± 207.9	366.9 ± 157.7	0.019
DA (mg/day)	224.6 ± 140.7	248.8 ± 171.0	240.5 ± 161.1	0.595

Depressed patients with PD were defined as SDS ≥ 40. Data are mean ± SD.
PD: Parkinson's disease, H&Y stage: Hoehn and Yahr stage, UPDRS: Unified Parkinson's Disease Rating Scale, PDSS: Parkinson's disease sleep scale, Levodopa/DCI: levodopa with decarboxylase inhibitor, DA: dopamine agonists, SDS: Zung Self-Rating Depression Scale.
[a] Chi-square test.

and age, gender, disease duration, PDSS, H&Y stage, UPDRS I, UPDRS II, UPDRS III, UPDRS IV, use of any DA, and use of levodopa/DCI as the independent variables identified PDSS ($p < 0.001$) and UPDRS I ($p = 0.002$) as significant determinants of SDS (Table 3). Another model, in which the SDS was used as the dependent variable, while sub-items of PDSS (items 1–15), age, gender, disease duration, H&Y stage, use of any DA, and use of levodopa/DCI were the independent variables, identified item 15 (daytime sleepiness) ($p = 0.002$), item 13 (early morning tremor) ($p = 0.008$), item 12 (nocturnal dystonia) ($p = 0.015$), and item 3 (sleep maintenance insomnia) ($p = 0.026$) as significant determinants of the SDS in PD patients (Table 4).

5. Discussion

In this study, depressive symptoms were observed in 64.9% of patients with PD. The higher prevalence rates for depressive symptoms compared with other study may be attributed to screening instrument or patient population. Although a number of studies have used various evaluation methods such as SDS, the Beck Depression Inventory, and the diagnostic criteria of Diagnostic and Statistical Manual of Mental Disorders-IV, the PD-specific evaluation method for depression is still lacking [20]. In SDS, sub-items such as fatigue, sleep disorders, and constipation may be based on the symptoms of PD itself, while items related to daily life and work may be affected by impairments of motor function. In addition, because the SDS is an evaluation tool that relies on the subject's own self-assessment, there is a tendency for overestimating depression in PD.

In neurobiological findings, postmortem examination of the brain of PD patients demonstrated 50–85% cell loss in the substantia nigra and locus ceruleus, 0–43% in the dorsal raphe nucleus and 32–87% cell loss in the basal nucleus of Meynert [21]. Thus, the depletion of endogenous neurotransmitters in the brain varies among patients with PD, suggesting that this variation may have an effect on varied prevalence rates for

Table 2
Total scores and sub-items of PDSS in Parkinson's disease and controls

	Controls	Non-depressed PD	Depressed PD	Total PD	p Value
Total	126.6 ± 17.8	123.2 ± 17.9	107.2 ± 27.1	112.8 ± 25.4	<0.001
Item 1	7.4 ± 3.1	7.2 ± 3.1	6.0 ± 3.5	6.4 ± 3.4	0.001
Item 2	7.9 ± 2.8	7.6 ± 3.4	7.2 ± 3.5	7.4 ± 3.4	0.316
Item 3	6.5 ± 3.2	6.5 ± 3.4	5.2 ± 3.8	5.7 ± 3.7	0.011
Item 4	9.2 ± 1.8	9.2 ± 1.9	8.2 ± 2.8	8.6 ± 2.6	<0.001
Item 5	9.1 ± 1.8	9.0 ± 2.1	8.1 ± 2.9	8.4 ± 2.7	<0.001
Item 6	9.0 ± 1.9	8.7 ± 2.1	7.4 ± 3.2	7.9 ± 2.9	<0.001
Item 7	9.6 ± 1.3	9.2 ± 2.1	8.1 ± 3.0	8.5 ± 2.8	<0.001
Item 8	5.3 ± 3.8	4.4 ± 3.9	4.1 ± 3.7	4.2 ± 3.8	0.045
Item 9	9.7 ± 1.4	9.1 ± 2.1	8.5 ± 2.6	8.7 ± 2.4	<0.001
Item 10	9.5 ± 1.6	9.4 ± 1.5	7.8 ± 3.3	8.4 ± 2.9	<0.001
Item 11	8.5 ± 2.3	9.0 ± 2.0	8.3 ± 2.5	8.5 ± 2.4	0.131
Item 12	9.5 ± 1.3	9.4 ± 1.3	8.0 ± 3.1	8.5 ± 2.7	<0.001
Item 13	9.8 ± 1.1	8.4 ± 2.7	6.9 ± 3.6	7.4 ± 3.4	<0.001
Item 14	7.6 ± 2.9	7.8 ± 3.0	6.6 ± 3.4	7.0 ± 3.3	0.012
Item 15	8.0 ± 2.6	8.3 ± 2.6	6.6 ± 3.4	7.2 ± 3.3	0.001

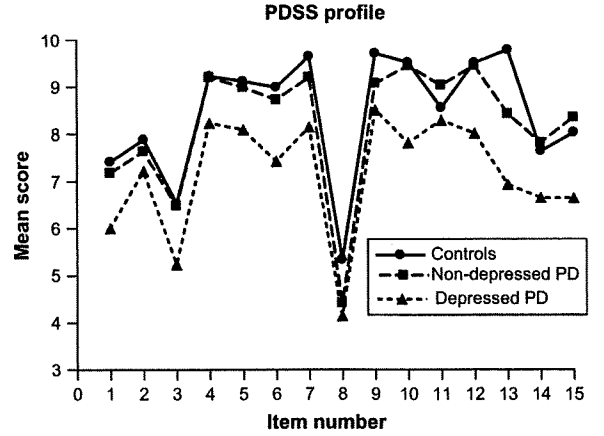

Fig. 1. Profiles of mean PDSS scores of sub-items in depressed PD, non-depressed PD and controls. Significant differences in PDSS sub-items except items 2 and 11 were seen among depressed patients, non-depressed patients, and controls.

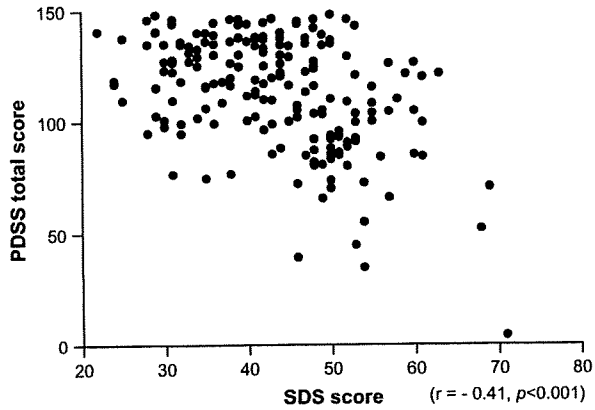

Fig. 2. Spearman's correlation analysis of SDS and PDSS in PD patients. Correlation coefficient = −0.41, $p < 0.001$.

depression in PD. As for the relationship between excessive daytime sleepiness, it has been demonstrated that bilateral destruction of ventral tegmental area (VTA) causes excessive daytime sleepiness in animal experiments [22] and PD patients with depression show greater dopamine loss in the mesolimbic dopaminergic pathway from VTA, as well as serotonin depletion in the dorsal raphe nucleus, noradrenalin depletion in the locus ceruleus, and acetylcholine depletion in the pedunculopontine nucleus and nucleus basalis of Meynert compared with patients without depression [23]. Moreover, it is believed that degeneration of cholinergic neurons and depletion of noradrenalin can cause disorders of rapid eye movement sleep, and serotonin depletion can reduce the amount of slow-wave sleep [24]. Based on these findings, PD patients with depression may show exacerbation of daytime sleepiness due to change in neurotransmitters.

In our study, Spearman's correlation analysis showed a significant correlation between depressive symptoms and nocturnal disturbances. Although depressed PD showed higher disease severity and severer motor dysfunction compared to non-depressed PD, motor function (UPDRS III) did not enter the final models as a significant variable in stepwise regression analysis with SDS. The results of stepwise regression analysis with SDS as the dependent variable identified PDSS and UPDRS I as significant determinants of the SDS. These findings support the previous reports that sleep disorders are exacerbated by depression in PD patients [3,25] and that cognitive dysfunction often complicates major depression [26]. We believe that depression, sleep disorders, and cognitive dysfunction interact with one another.

Table 3
Stepwise regression analysis of SDS in Parkinson's disease

Parameter	Clinical variable	R^2
SDS	PDSS	0.200
	PDSS + UPDRS I	0.301

SDS was used as the dependent variable, while age, gender, disease duration, PDSS, H&Y stage, UPDRS I, UPDRS II, UPDRS III, UPDRS IV, use of levodopa/DCI, and use of any DA were independent variables.
For abbreviations, see Table 1.

Table 4
Stepwise regression analysis of SDS in Parkinson's disease (including subitems of PDSS)

Parameter	Clinical variable	R^2
SDS	Item 15	0.108
	Item 15 + item 13	0.168
	Item 15 + item 13 + item 12	0.196
	Item 15 + item 13 + item 12 + item 3	0.218

SDS was used as the dependent variable, while age, gender, disease duration, PDSS (items 1–15), H&Y stage, use of any DA, and use of levodopa/DCI were independent variables.
Item 15: daytime sleepiness, item 13: early morning tremor, item 12: nocturnal dystonia, item 3: sleep maintenance insomnia.

Happe et al. [3] reported significant correlations between SDS and the narcolepsy score and periodic limb movement disorder score (including items regarding restless legs syndrome) in their study of 56 patients with PD and 59 control subjects. On the other hand, in our study, daytime sleepiness and sleep maintenance insomnia and the causes thereof, including early morning tremors and nocturnal paroxysmal dystonia, correlated with the SDS (depressive symptoms) in PD. It is widely believed that sleep maintenance insomnia is more common than difficulty in falling asleep in patients with PD [1]. Because sleep maintenance insomnia was closely associated with depressive symptoms in this study, we consider depression to be associated with nocturnal symptoms, or it may potentially be due to abnormality of the structures involved in sleep regulation caused by the disease process itself.

Dhawan et al. [9] compared nocturnal disturbances among 59 cases of PD (25 cases were untreated and 34 cases were treated) and 131 control subjects using PDSS. The results showed that nocturia, nighttime cramps, dystonia, tremors, and daytime somnolence were important factors for untreated PD. However, these symptoms were similar to the nocturnal symptoms that are important to PD with severe depressive symptoms in our study, they did not include a description of depressive symptoms. It has been reported that dystonia and tremors in PD increase in the "off" state, and depression exacerbates nocturnal off-period-related motor symptoms [2]. Furthermore, depression is reported to trigger the "wearing off", and a hypodopaminergic state and a psychological "off" have been considered as causes for this phenomenon [27].

With regard to the relationship between dystonia and nocturnal symptoms, Lees et al. [28] found dystonia in 34% of 215 cases of PD, and Starkstein et al. [25] reported that depression was the most important factor associated with sleep disorders and pain. Goetz et al. [29] discussed the possibility that depression changes the interpretation of pain and the possibility that depression exacerbates pain, because pain was frequently observed in patients with severe depression among 95 cases of PD. Animal experiments have shown that tremors are due to depletion of the neostriatal content of serotonin and dopamine [30], while clinical studies indicated that bradykinesia and rigidity are more severe than tremors as characteristics of motor function in depressed PD [2]. Conversely, early morning tremors were closely associated with the depressive state in

our study, and this is believed to be due to nocturnal off-period-related symptoms rather than daytime motor function.

In conclusion, there was a significant correlation between patients with depressive symptoms and nocturnal disturbances. We demonstrate that nocturnal disturbances and cognitive dysfunction were significant determinants of depressive symptoms and that daytime sleepiness, dystonia, tremor and sleep fragmentation seem to be the important nocturnal disturbances in depressed patients with PD.

Appendix 1. The Parkinson's disease sleep scale (from Ref. [6])

Item 1 The overall quality of your night's sleep is:
Item 2 Do you have difficulty falling asleep each night?
Item 3 Do you have difficulty staying asleep?
Item 4 Do you have restlessness of legs or arms at night or in the evening causing disruption of sleep?
Item 5 Do you fidget in bed?
Item 6 Do you suffer from distressing dreams at night?
Item 7 Do you suffer from distressing hallucination at night (seeing or hearing things that you are told do not exist)?
Item 8 Do you get up at night to pass urine?
Item 9 Do you have incontinence of urine because you are unable to move due to "off" symptoms?
Item 10 Do you experience numbness or tingling of your arms or legs which wake you from sleep at night?
Item 11 Do you have painful muscle cramps in your arms or legs whilst sleeping at night?
Item 12 Do you wake early in the morning with painful posturing of arms or legs?
Item 13 On waking do you experience tremor?
Item 14 Do you feel tired and sleepy after waking in the morning?
Item 15 Have you unexpectedly fallen asleep during the day?

For question 1: Awful = 0, Excellent = 10. For question 15: Frequently = 0, Never = 10. For the remaining of the questions: Always = 0, Never = 10.

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INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Predictors of a Prolonged Clinical Course in Adult Patients with Herpes Simplex Virus Encephalitis

Naoto Taira, Satoshi Kamei, Akihiko Morita, Masaki Ishihara, Kenji Miki, Hiroshi Shiota and Tomohiko Mizutani

Abstract

Objective Herpes simplex virus encephalitis (HSVE) patients occasionally follow a prolonged course despite standard antiviral treatment. The purpose of this study was to analyze clinical variables to identify predictors of a prolonged course.

Methods A series of 23 HSVE patients treated with acyclovir (ACV) during the acute stage were selected and divided into 2 groups: the non-prolonged group (n = 15), with improvement within 2 weeks after initial ACV treatment; and the prolonged group (n = 8), without improvement within 2 weeks. Differences in clinical variables, including age, duration from onset to initial ACV treatment, Glasgow coma scale (GCS) score, corticosteroid administration, detection of abnormal lesions on initial cranial computed tomography (CT) and magnetic resonance imaging, detection of periodic lateralized epileptiform discharges on electroencephalogram, and clinical outcome, were compared between the groups.

Results There were significant differences in GCS score, clinical outcome, and detection of lesions on CT between the non-prolonged and prolonged groups [p = 0.021, p = 0.041 (Mann-Whitney's U test), respectively, and p = 0.027 (Fisher's exact test)]. Four of the eight patients with a prolonged course had a poor outcome despite treatment with additional drugs.

Conclusion A lower GCS and a higher rate of lesions on CT were identified as predictors of a prolonged course for HSVE. These predictors are in accordance with the conventional predictors of poor outcome for HSVE. This study suggests that the initial ACV treatment was insufficient for HSVE patients with these predictors at the acute stage. The initial treatment may need to be modified for such patients.

Key words: outcome, prolonged, predictor, herpes simplex virus encephalitis

(Inter Med 48: 89-94, 2009)
(DOI: 10.2169/internalmedicine.48.1445)

Introduction

Herpes simplex virus (HSV) is a human herpes virus that can cause HSV encephalitis (HSVE), the most common, serious, sporadic, viral encephalitis in humans (1). HSVE patients who do not receive antiviral treatment have an extremely high mortality rate (about 70%), and fewer than 3% of survivors return to normal function (1, 2). Of the common central nervous system (CNS) viral infections, HSVE has a disproportionately high mortality compared with encephalitis due to other viruses. The introduction of acyclovir (ACV) has dramatically improved mortality and morbidity for patients with HSVE (2, 3); mortality rates for HSVE have decreased to 19 - 28% (2, 3). Although ACV treatment for HSVE is highly effective, the rate of poor outcome including advanced sequelae remains high, at 30 - 50%, and the rate of return to normal living is less than 50% (1-3). Thus, the morbidity and mortality remain significantly high for HSVE despite standard ACV treatment at the acute stage.

Conventional predictors of poor outcome for HSVE have been reported to include the following 5 factors: age over 30 years, duration of more than 4 days from onset to the initiation of antiviral treatment, Glasgow Coma Scale (GCS) score of 6 points or less, detection of abnormal lesions on

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Received for publication June 23, 2008; Accepted for publication September 3, 2008
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cranial computed tomography (CT) at initiation of antiviral treatment, and the detection of more than 100 copies/mL of HSV-DNA by polymerase chain reaction (PCR) in the initial cerebrospinal fluid (CSF) (2, 4-6). Management of patients with these predictors of poor outcome is difficult, and some patients with HSVE follow a prolonged course even with appropriate ACV treatment. Thus, further improvements in therapeutic regimens are needed for patients with HSVE.

Several previous reports have described relapses of HSVE in pediatric (7-10) and adult patients (3, 11-15), but there have been no previous studies involving adult HSVE patients who had a prolonged course and did not improve significantly despite standard ACV treatment. Therefore, the details of the clinical course were studied in adult HSVE patients with a prolonged course. The present study is the first to evaluate the clinical predictors in HSVE patients with a prolonged course despite standard ACV treatment.

Patients and Methods

The subjects consisted of HSVE patients treated with ACV during the acute stage. A series of patients with HSVE were selected from among all HSVE patients admitted to Nihon University Itabashi Hospital in Tokyo, Japan, between 1996 and 2007. To evaluate predictors of a prolonged course in adult HSVE patients, diagnostic and therapeutic protocols were established in advance, as reported previously (16). In this diagnostic protocol, the etiological diagnosis of HSVE was based on positive results from the following three laboratory tests: nested or real-time PCR; specific intrathecal HSV antibody synthesis; and chemiluminescence assay (17). The patients were treated according to the clinical guideline of herpes simplex encephalitis in Japan, which consisted of intravenous ACV (30 mg/kg/day) for 14 days from the time of admission (18). The therapeutic protocol permitted the use of corticosteroids at the discretion of the patients' treating physicians, although it did not specify the dosage or duration of corticosteroid treatment. When used, corticosteroids were started at the same time that ACV treatment was started. The selected patients were treated according to our therapeutic protocol, which consisted of intravenous ACV for 14 days starting at the time of admission. HSVE patients who were not treated with ACV in the acute stage were excluded. The selected patients were divided into 2 groups: the non-prolonged group, which was defined as patients who showed improvement within 2 weeks after initiation of ACV treatment without deterioration; and the prolonged group, which was defined as patients without any neurological improvement at the time of completion of the administration of ACV for 14 days. When the standard treatment failed, the patients were given additional treatment, such as extended ACV treatment, or adenine arabinoside (Ara-A), or combination therapy with both ACV and Ara-A. The clinical, neuroradiological, and neurophysiological parameters were compared between these groups in order to identify the predictors of a prolonged course in HSVE patients.

To assess differences between the groups, several parameters were studied. Clinical parameters that were extracted from the medical records of adult HSVE patients were: 1) sex (m = male, f = female); 2) age (years); 3) presence or absence of a prolonged course (absent = 0, present = 1); 4) duration from onset of HSVE to initiation of ACV treatment (days); 5) GCS at the start of ACV treatment; 6) corticosteroid administration (given = 0, not given = 1); and 7) clinical outcome. The clinical outcome was classified into five groups as reported previously (19), and categorized as follows: complete recovery = 0; mild sequelae = 1, for patients with minor neuropsychological deficits; moderate sequelae = 2, for patients with limitations due to motor, speech, memory, or seizure disorders; severe sequelae = 3, for patients requiring supportive care; and death = 4. The clinical outcomes were assessed three months after the completion of ACV treatment in the same way as described previously (19).

Neuroradiological and neurophysiological parameters included: 8) detection of focal lesions on initial cranial CT (initial CT examinations were performed in all subjects within 24 hours after admission; absent = 0, present = 1); 9) detection of abnormal lesions on initial magnetic resonance imaging (MRI; absent = 0, present = 1); and 10) detection of periodic lateralized epileptiform discharges (PLEDs) on the initial electroencephalogram (EEG; absent = 0, present = 1).

All continuous variables are expressed as minimum, mean, median, and maximum, and differences between groups were assessed using Mann-Whitney's U test. All categorical variables are expressed as percentages, and differences were assessed using Fisher's exact test. Values of $p < 0.05$ were considered statistically significant. Statistical analyses were performed using SPSS™ for Windows software, version 15 (SPSS, Chicago, IL, USA).

All of the patients and/or their families gave their written informed consent to participate in the study according to a protocol approved by the Ethics Committee for Human Studies at Nihon University Itabashi Hospital.

Results

A series of 23 HSVE patients was selected from a total of 32 HSVE patients. The 23 patients included 14 men and 9 women, and their ages ranged from 17 to 77 years (average age, 46.4±19.9 years). Nine patients who were treated with Ara-A therapy and did not receive ACV during the acute stage were excluded. The clinical data, including treatments and clinical outcomes, of the 23 patients are shown in Table 1. The patients were divided into the non-prolonged group [n=15 (65.2%); patients 1 to 15 in Table 1] and the prolonged group [n = 8 (34.8%); patients 16 to 23 in Table 1]. The prolonged group patients received additional antiviral therapies: 1 patient was treated with Ara-A (patient 17); 3 patients were treated with extended ACV treatment (patients 18, 20, and 21); and 4 patients were treated with

Table 1. Clinical Data of the 23 Patients with Herpes Simplex Virus Encephalitis Included in the Present Study

Patient No	Sex	Age (years)	Prolonged course	Days from onset to initial ACV	GCS score at initial ACV	Initial CSF leukocyte cell count (/μL)	Initial CSF protein (mg/dL)	Additional treatment	Corticosteroid administration	Detection of lesions on initial brain CT	Detection of abnormal lesions on initial brain MRI	Detection of PLEDs on EEG	Outcome score
A. Non-prolonged group													
1	m	74	0	2	6	52	33	None	0	1	1	1	2
2	m	19	0	10	7	149	120	None	0	1	1	1	0
3	f	20	0	3	10	9	33	None	0	0	0	1	1
4	f	24	0	4	12	362	40	None	1	0	0	0	0
5	f	34	0	5	15	820	398	None	1	0	0	0	0
6	m	36	0	10	10	16	88	Ara-A	0	0	1	0	0
7	f	53	0	7	11	458	189	Extend ACV	1	1	1	1	2
8	m	56	0	2	12	503	37	None	0	0	1	1	1
9	m	77	0	1	12	571	580	None	0	0	1	0	1
10	f	77	0	3	4	7	88	None	0	1	1	0	2
11	m	27	0	4	13	21	45	None	1	1	1	0	0
12	m	32	0	5	13	253	171	None	0	0	0	0	0
13	m	54	0	4	11	9	38	Extend ACV	0	0	1	0	1
14	f	76	0	6	6	7	24	Extend ACV	1	0	1	0	2
15	f	61	0	3	15	315	97	None	0	0	0	0	0
B. Prolonged group with good clinical outcome													
16	m	28	1	5	12	236	115	Extend ACV +Ara-A	1	0	1	0	0
17	m	17	1	4	7	139	104	Ara-A	0	1	1	1	1
18	f	28	1	5	3	4	77	Extend ACV	0	1	1	1	1
19	f	53	1	1	6	45	72	Extend ACV +Ara-A	0	1	1	1	1
C. Prolonged group with poor outcome													
20	m	66	1	5	3	56	85	Extend ACV	1	1	1	0	3
21	m	57	1	7	3	944	410	Extend ACV	1	1	1	0	4
22	m	59	1	2	12	5	40	Extend ACV +Ara-A	0	1	1	1	4
23	m	45	1	7	4	3	70	Extend ACV +Ara-A	1	1	1	1	4

GCS, Glasgow coma scale; CT, computed tomography; MRI, magnetic resonance imaging; ACV, acyclovir; Ara-A, adenine-arabinoside; PLEDs, periodic lateralized epileptiform discharges; EEG, electroencephalogram; m, male; f, female; Corticosteroid administration: 0 = given; 1 = not given; Detection of lesions on initial brain CT and MRI: 0 = absent; 1 = present; Detection of PLEDs on EEG: 0 = absent; 1 = present; Outcome score: 0 = complete recovery; 1 = mild sequelae; 2 = moderate sequelae; 3 = severe sequelae; 4 = death; Prolonged course, 0 = absent; 1 = present; Additional treatment gives the name of the antiviral drug that was administered after ACV treatment for 14 days. Extend ACV indicates extension of the duration of ACV administration.

both (patients 16, 19, 22, and 23). Of these 8 patients, 2 (patients 22 and 23) of the 4 patients who received both additional treatments after initial ACV died, and 2 (patients 20 and 21) of the 3 patients with extended ACV treatment had poor outcomes (Table 1). Despite the administration of additional antiviral treatments, the clinical outcome was poor in 50% (4 patients, Nos. 20 to 23) of prolonged group patients, including 3 patients (patients 21 to 23) who died. Patient 21 died of HSVE, and patients 22 and 23 died of multiple organ failure. However, the 4 remaining patients (patients 16 to 19) had a good outcome.

Differences in the clinical characteristics between the non-prolonged and prolonged groups and the results of the statistical analyses are shown in Table 2. The mean GCS score at the time of the initial ACV treatment was 6.3 in the prolonged group and 10.5 in the non-prolonged group; the GCS score was significantly lower in the prolonged group than in the non-prolonged group ($p = 0.021$, Mann-Whitney's U test). The rate of abnormal lesions on cranial CT at the time of the initial ACV treatment was 87.5% in the prolonged group and 33.3% in the non-prolonged group; thus, abnormal lesions on cranial CT were significantly more common in the prolonged group than in the non-prolonged group ($p = 0.027$, Fisher's exact test). The mean clinical outcome score was 2.25 in the prolonged group and 0.8 in the non-prolonged group; thus, the clinical outcome score was significantly worse in the prolonged group than in the non-prolonged group ($p = 0.041$, Mann-Whitney's U test). No other variables showed significant differences between the groups. The prolonged group was thus characterized as having a lower GCS score at the start of ACV treatment, a higher rate of abnormal lesions on initial cranial CT, and a poorer outcome score.

Discussion

In the present study, compared to HSVE patients in the non-prolonged group, HSVE patients in the prolonged group had a lower GCS score at the start of ACV treatment, a higher rate of abnormal lesions on initial cranial CT, and a poorer clinical outcome score. A lower GCS score and a higher rate of abnormal lesions on initial cranial CT in the

Table 2. Baseline Clinical Characteristics by Patient Group (Prolonged or Non-prolonged Course)

	Prolonged course (n = 8)	Non-prolonged course (n = 15)	p
(1) Male (%)	75.0	53.3	1.00
(2) Age (minimum, mean, median, and maximum: years)	17.0, 44.1, 49.0, 66.0	19.0, 47.6, 53.0, 77.0	0.693
(3) Days from onset to initiation of ACV (minimum, mean, median, and maximum)	1.0, 4.5, 5.0, 7.0	1.0, 4.6, 4.0, 10.0	0.776
(4) GCS score at initiation of ACV (minimum, mean, median, and maximum)	3.0, 6.3, 5.0, 12.0	4.0, 10.5, 11.0, 15.0	0.021*
(5) Corticosteroid administration (%)	50.0	66.7	0.657
(6) Detection of lesions on initial CT (%)	87.5	33.3	0.027*
(7) Detection of lesions on initial MRI (%)	100.0	66.7	0.112
(8) Detection of PLEDs on EEG (%)	62.5	33.3	0.221
(9) Clinical outcome score (0 = complete recovery; 1 = mild sequelae; 2 = moderate sequelae; 3 = severe sequelae; 4 = death) (minimum, mean, median, and maximum)	0, 2.25, 2.0, 4.0	0, 0.8, 1.0, 2.0	0.041*

GCS, Glasgow coma scale; CT, computed tomography; MRI, magnetic resonance imaging; PLEDs, periodic lateralized epileptiform discharges; EEG, electroencephalogram. Continuous variables were compared using Mann-Whitney's U test. Categorical variables were compared using Fisher's exact test. *$p < 0.05$

prolonged group are also in accordance with the conventional predictors of poor outcome for HSVE (2, 4, 5). In the prolonged group, the average GCS score was 5.5 with a poor outcome and 7.0 with a good outcome. The GCS score of the prolonged group with a poor outcome tended to be lower than that with a good outcome. 87.5% of prolonged group patients had abnormal lesions on CT.

According to a previous study, abnormal lesions, such as a low density lesion in the temporal lobe, became distinct and spread as the clinical features progressed (20). Therefore, the prolonged group already had progression during the period of initial treatment compared to the non-prolonged group. MRI is reported to be a useful tool and superior to CT for early detection of abnormal lesions (21), and most HSVE patients in the present study showed abnormal lesions on MRI; this may explain why the detection rate of lesions on MRI was not significantly different between the two groups.

The therapeutic management of HSVE has been established (22), but it is still considered to be unsatisfactory in some patients. HSVE patients occasionally show a relapse or have a prolonged course; patients who had a relapse were not included in the present study. With respect to relapse, several studies have been reported (3, 7-15). In the previous studies, the frequency of relapse after HSVE ranged from 5% to 26% (8-10), with pediatric patients having higher relapse rates. In a report of a series of 27 children with acute HSVE, 7 patients (26%) had a relapse of HSVE, and 5 of the 7 improved with repeated, high-dose ACV (30 - 45 mg/kg/day) treatment, although 3 of the 5 patients developed moderate to severe sequelae (9). In other reports, 4 of 32 (13%) adult HSVE patients had a relapse. These 4 patients were treated with additional ACV (30 mg/kg /day) at the time of relapse, but 3 of the 4 patients developed moderate to severe sequelae (15). According to these studies, a low initial dose of ACV has been reported to be frequently associated with HSVE relapse (9, 15). Although the duration of the original ACV trial (2) was 10 days, most physicians currently continue therapy for 14 - 21 days to reduce the risk of relapse (3, 14, 22). A recently published clinician's guide for HSVE (22) recommends the continuous administration of ACV if HSV-DNA is still detected on PCR at the end of initial ACV treatment.

In contrast to relapses, HSVE patients with a prolonged course have not been studied previously. In the present study, 8 of 23 HSVE patients had a prolonged course despite standard ACV treatment (30 mg/kg/day for 14 days) at the time of admission, and additional treatment with antivi-

ral drugs (ACV, Ara-A, or both) was ineffective in 4 (patients 20 to 23 in Table 1) of the 8 patients, though it was effective in the remaining 4 (patients 16 to 19 in Table 1).

The pathophysiological findings associated with prolonged HSVE remain unclear. Prolongation of HSVE was considered to be introduced by insufficient HSV inhibition, secondary encephalitis, or both. Insufficient HSV inhibition resulted from an insufficient ACV dose and/or the presence of ACV-resistant HSV. Considering that 8 out of 23 patients had a prolonged course despite initial standard ACV treatment in the present study (18), this initial treatment might have been insufficient to inhibit HSV infection for patients with a prolonged course. On the other hand, it has been reported that levels of pro-inflammatory cytokines in the CSF of HSVE patients were high (23), and HSV was not always detected by PCR at the time of relapse in the CSF of relapsed pediatric patients with HSVE (9). These reports suggested that prolongation of HSVE might be also caused by secondary encephalitis based on the host immune response. In the present study, corticosteroid treatment was given to 50% of prolonged group patients and 66.7% of non-prolonged group patients. Corticosteroid treatment was not significantly different between the groups, but 10 of 14 patients given corticosteroids did not have a prolonged course. Therefore, corticosteroid treatment may have a beneficial protective effect against secondary encephalopathy based on the host immune response in HSVE (23). Since our previous retrospective study showed that corticosteroid treatment improved the outcome of HSVE (16), this suggested the need for further investigation to determine whether corticosteroid treatment had the potential to protect against HSVE progression.

The prolonged group patients had a poorer clinical outcome than the non-prolonged group patients. Therefore, initial antiviral treatment may need to be modified in patients who have the predictors for a prolonged course, and this may improve their clinical outcome. The possible modifications of the initial antiviral treatment may include high-dose ACV treatment or combination ACV and Ara-A therapy in patients with the predictors of a prolonged course.

In conclusion, 2 predictors of a prolonged course were identified in HSVE patients: a lower GCS score at the start of antiviral treatment and a higher rate of abnormal lesions on initial CT. Since the number of patients was small in the present study, further investigation is required to assess the predictors of clinical outcome using multivariate analysis in a larger number of HSVE patients.

Acknowledgement

The present work was supported by a grant from the Ministry of Education, Culture, Sports, Science and Technology of Japan for the promotion of industry-university collaboration at Nihon University, Japan, and a Research Grant (18A-9) for Nervous and Mental Disorders from the Ministry of Health, Labour and Welfare, Japan.

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INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Hospital-Based Study of the Prognostic Factors in Adult Patients with Acute Community-Acquired Bacterial Meningitis in Tokyo, Japan

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Abstract

Background Prognostic factors related to community-acquired bacterial meningitis (BM) in adult patients have been evaluated using multivariate analysis in the Netherlands, where the rate of antibiotic resistance was low. However, an evaluation of these factors in countries with a high rate of antibiotic resistance has not yet been done. Thus, we studied the prognostic factors in adults with community-acquired BM in our hospitals, which are located in Tokyo, Japan, where the rate of antibiotic resistance is high.

Methods We selected 71 consecutive adult patients with community-acquired BM in which the pathogens were identified and then classified the patients into two groups based on the Glasgow Outcome Scale: a favorable outcome group (n=48), and an unfavorable outcome group (n=23). Their clinical and laboratory variables were analyzed using single logistic regression analysis followed by multiple logistic regression analysis.

Results The overall mortality rate was 23%. The rate of antibiotic resistance was 54.9%. The most common resistant bacteria were penicillin-resistant *Streptococcus pneumoniae*, followed by methicillin-resistant *Staphylococcus aureus*. The Glasgow Coma Scale score (GCS) at the initiation of antibiotic therapy and a low thrombocyte count were identified as significant unfavorable prognostic factors (GCS: p=0.020, odds ratio=0.528, 95%CI=0.309-0.902; thrombocyte count: p=0.037, odds ratio=0.802, 95%CI=0.652-0.987). The presence of antibiotic-resistant bacteria was not identified as a prognostic factor.

Conclusion Patients with a low GCS at the initiation of antibiotic therapy and low thrombocyte counts had unfavorable outcomes. With appropriate antibiotic administration, the antibiotic-resistant bacteria were not identified as an unfavorable prognostic factor, even in an area with a high rate of antibiotic resistance.

Key words: prognostic factor, adult, antibiotic resistance, bacterial meningitis, Japan

(Inter Med 48: 295-300, 2009)
(DOI: 10.2169/internalmedicine.48.1508)

Introduction

In Japan, there are approximately 1,500±400 patients with bacterial meningitis (BM) each year, of which 29% have been estimated to be adults (1). Despite the progress in antibiotic therapy, the mortality rate of BM still remains at 15-35% (2-5), and the rate of sequelae remains at 10-30% (4-6). BM is considered a neurological emergency. It is important to define the prognostic factors associated with an unfavorable outcome in order to control the disease with early diagnosis and adequate treatment. A between-groups comparative analysis was used in the majority of previous studies dealing with prognostic factors in adult patients with community-acquired BM (3, 4, 6-12). Recently, prognostic factors were evaluated in 696 patients with BM in the Netherlands using multiple logistic analyses (5). In a previous study (5), the rate of antibiotic resistance to penicillin was

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Received for publication July 14, 2008; Accepted for publication October 23, 2008
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reported to be very low. In the discussion section of the study, it was described as follows: "Rates of antibiotic resistance in this study were very low. In the United States, France, Spain, and other countries, antibiotic-resistant *Streptococcus pneumoniae* strains are highly prevalent and have emerged as a major problem in the treatment of patients with BM. The relationship of antibiotic resistance to the outcome of meningitis remains to be elucidated." Therefore, the aim of the present study was to evaluate the prognostic factors in adults with BM through multiple logistic analyses at our hospitals, which are located in Tokyo, Japan, where the prevalence of antibiotic resistance is high.

Patient and Methods

The data of adult patients with clinical symptoms and laboratory data, including cerebrospinal fluid (CSF) findings, compatible with BM who were admitted to our hospitals (Nihon University Itabashi Hospital and Surugadai Hospital), which are located in Tokyo, Japan, during the period from April 1998 to December 2007 were retrospectively reviewed. Patients who were diagnosed by the identification of pathogens by Gram staining of CSF, culture-positive CSF, positive polymerase chain reaction (PCR) results, or any combination of these factors were selected. Patients with suspected BM in whom pathogens were not identified were excluded. Thus, 71 consecutive adult patients with community-acquired BM entered this study. They were classified into five grades according to the Glasgow Outcome Scale (GOS), as reported previously (5, 13): V, normal; IV, mild sequelae for patients with minor neuropsychological deficits; III, moderate sequelae for patients with limitations due to motor, speech, memory, or seizure disorders; II, severe sequelae for patients requiring supportive care; I, death. The selected patients were further classified into two groups: a favorable outcome, consisting of GOS grade V, and an unfavorable outcome, consisting of GOS grades I to IV. To evaluate the differences between the two groups, 16 potentially relevant predictors were chosen based on previous research (5) and pathophysiologic interest. They included: 1) sex, 2) age, 3) duration from onset to the initiation of antibiotic therapy aimed at BM pathogens, 4) Glasgow coma scale (GCS) score at the initiation of antibiotic therapy, 5) diastolic blood pressure of less than 60 mmHg, 6) thrombocyte count, 7) serum C reactive protein value, 8-10) CSF findings [8) cell count, 9) protein, and 10) glucose concentrations], 11) seizures, 12) immunocompromised status (chronic alcoholism, malignancies not in remission, diabetes mellitus, chronic immunosuppressive therapy, terminal renal failure, chronic hepatitis with liver cirrhosis, and history of splenectomy), 13) corticosteroid administration, 14) positive blood culture, 15) *Streptococcus pneumoniae*, and 16) presence of antibiotic-resistant bacteria.

Statistical analysis

In January 2008, the data for the clinical and laboratory variables were collected from the patients' medical records. The data were compared between the favorable and unfavorable outcome groups in order to evaluate the prognostic factors associated with an unfavorable outcome. Statistical analyses were performed using SPSS™ for Windows software, version 15 (SPSS, Chicago, IL, USA). Dichotomous dependent variable recovery was assigned a value of 0 when the outcome was favorable and 1 when unfavorable. All continuous variables are expressed as minimum, mean, median, and maximum. All categorical variables are expressed as percentages. Single variable logistic regression analysis was used to examine the significance of the independent variables with respect to the outcome. Only variables that were significant at $p<0.10$ were tested in backward stepwise multiple logistic regression analysis using maximum likelihood estimation. The relationship between the GOS and the presence of antibiotic-resistant bacteria was assessed using Fisher's exact test. Values of $p<0.05$ were considered statistically significant. All of the patients gave their written informed consent to participate in the study according to a protocol approved by the Research Review Board at Nihon University Itabashi Hospital.

Results

The outcome of 71 consecutive patients with BM was favorable in 48 (68%) and unfavorable in 23 (32%). The clinical variables of the groups with favorable and unfavorable outcomes, as well as the results of single logistic regression analyses for prognostic factors in BM, are listed in Table 1. The patients consisted of 45 men (63%) and 26 women (37%), with a mean age of 53 years (range, 10-84 years). The overall mortality rate was 23%. In single variable logistic regression analysis, the following factors were associated with outcome at $p<0.05$: age ($p=0.006$, odds ratio=1.058, 95%CI=1.016-1.101), GCS score ($p<0.001$, odds ratio=0.703, 95%CI=0.595-0.831), thrombocyte count ($p=0.003$, odds ratio=0.833, 95%CI=0.738-0.939), immunocompromised status ($p=0.018$, odds ratio=4.370, 95%CI=1.293-14.771), and positive blood culture ($p<0.001$, odds ratio=14.25, 95%CI=4.039-50.272).

The bacteria isolated from the CSF are listed in Table 2. It is important to note that 60.6% of our 71 patients had taken antibiotics before admission. The most common pathogen detected in the CSF was *Streptococcus pneumoniae*, followed by *Staphylococcus aureus*. Bacteria resistant to any antibiotic drugs were detected in 39 patients (54.9%). The most common resistant bacteria were penicillin-resistant *Streptococcus pneumoniae* (PRSP), followed by methicillin-resistant *Staphylococcus aureus* (MRSA). PRSP and penicillin-intermediate *Streptococcus pneumoniae* (PISP) were present in 20% of all patients. There was no significant association between the GOS and the presence of antibiotic-resistant bacteria ($p=0.15$); in the analysis of selected patients with BM due to *Streptococcus pneumoniae* or *Staphylococcus aureus*, there was also no significant asso-

Table 1. The Clinical Variables and the Results of Single Logistic Regression Analyses for Prognostic Factors in BM

	All episodes of BM (n=71)	Favorable outcome (n=48)	Unfavorable outcome (n=23)	p value	Odds ratio <95%CI>
(1) Male (%)	63	65	61	0.761	
(2) Age (minimum, mean, median, and maximum: years)	10, 53.0, 59.0, 84	10, 48.6, 52.5, 84	32, 62.2, 63, 79	0.006*	1.058 <1.016-1.101>
(3) Duration from onset to the initiation of the antibiotic therapy (minimum, mean, median, and maximum: days)	0, 3.38, 2.0, 27	0, 3.81, 2, 27	0, 2.48, 1, 10	0.245	
(4) GCS score (minimum, mean, median, and maximum)	3, 10.35, 12.0, 15	4, 11.85, 12, 15	3, 7.22, 6, 15	<0.001*	0.703 <0.595-0.831>
(5) Diastolic blood pressure < 60 mmHg (%)	5	0	14	0.704	
(6) Thrombocyte count (minimum, mean, median, and maximum: $\times 10^4/\mu L$)	0.4, 13.88, 10.70, 43	1, 18.18, 16.45, 43	0.4, 6.36, 4.75, 19	0.003*	0.833 <0.738-0.939>
(7) Serum C reactive protein (minimum, mean, median, and maximum: mg/dL)	0.1, 15.84, 15.30, 54.7	0.3, 14.70, 15, 37.7	0.1, 18.23, 17.4, 54.7	0.219	
(8) CSF cell count (minimum, mean, median, and maximum: /μL)	2, 3703.17, 961, 85333	13, 2581, 893, 21733	2, 6046, 1050, 85333	0.306	
(9) CSF protein (minimum, mean, median, and maximum: mg/dL)	29, 347.27, 188, 4483	29, 380.31, 211, 4483	43, 278.3, 171, 779	0.499	
(10) CSF glucose (minimum, mean, median, and maximum: mg/dL)	1, 47.54, 28.0, 484	1, 45.7, 39, 185	1, 51.39, 19, 484	0.080	
(11) Seizures (%)	14	13	17	0.581	
(12) Immunocompromised status (%)	62	52	83	0.018*	4.370 <1.293-14.771>
(13) Corticosteroid administration (%)	65	63	70	0.560	
(14) Positive blood culture (%)	44	25	83	<0.001*	14.25 <4.039-50.272>
(15) *Streptococcus pneumoniae* (%)	28	27	30	0.769	
(16) Antibiotic-resistant bacteria (%)	55	48	70	0.090	

BM = bacterial meningitis; CI = confidence interval; GCS= Glasgow Coma Scale; CSF= cerebrospinal fluid; * = statistically significant ($p<0.05$).

Table 2. Bacteria Isolated from the CSF (n=71)

	Number identified	Ratio of antibiotic-resistant bacteria for each strain
Staphylococcus	23	
MRSA	7	30.4 %
Penicillin-resistant *Staphylococcus aureus*	4	17.4 %
Staphylococcus aureus	5	
Others	7	8.7 %
Streptococcus	29	
Streptococcus pneumoniae		
PSSP	6	
PISP	3	10.3 %
PRSP	11	37.9 %
Others	9	31.0 %
Campylobacter fetus	5	20 %
Klebsiella pneumoniae	4	75 %
Haemophilus influenzae	4	75 %
Listeria monocytogenes	2	
Other pathogens	4	75 %

The category of 'Other pathogens' includes *Enterococcus, Bacteroides fragilis,* and *Pseudomonas aeruginosa.*
MRSA, methicillin-resistant *Staphylococcus aureus*; PSSP, penicillin-sensitive *Streptococcus pneumoniae*
PISP, penicillin-intermediate sensitive *Streptococcus pneumoniae*; PRSP, penicillin-resistant *Streptococcus pneumoniae*

ciation (p=0.63, p=0.88, respectively). Patients with BM caused by PRSP/PISP were treated with vancomycin and/or carbapenem antibiotics. Patients with BM caused by MRSA were treated with vancomycin and/or aminoglycoside antibi-