

Original Article

무균성수막염과 뇌염환자 사이의 인구학과 검사소견의 비교: 나이와 C-반응단백질의 중요성

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Comparison of the Demographic and Laboratory Profiles of Patients with Aseptic Meningitis and Encephalitis: Significance of Age and C-reactive Protein

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Background: Viruses can cause either meningitis or encephalitis. It is unclear why some people suffer from aseptic meningitis, and others acquire aseptic encephalitis when infected with the same viral pathogens. The aim of this study was to compare demographic and laboratory factors between patients with aseptic meningitis and encephalitis. **Methods:** The demographic and laboratory differences were analyzed according to age, sex, diabetes, hypertension, C-reactive protein in the blood, white blood cell and protein in the cerebrospinal fluid, and glucose ratio (cerebrospinal fluid/blood). Additionally, we analyzed the nation-wide differences in age between the patients with aseptic meningitis and those with encephalitis in Korea. **Results:** The patients with aseptic encephalitis were older, more likely to have hypertension, and had higher levels of C-reactive protein than did the patients with aseptic meningitis. However, the numbers of white blood cells in the cerebrospinal fluid were significantly higher in the patients with meningitis than in the patients with encephalitis. Multivariable analysis revealed that age >49 years, hypertension and a C-reactive protein level >5.81 mg/dL were independent and significant variables in the prediction of aseptic encephalitis. Additionally, the patients with aseptic encephalitis were older than those with aseptic meningitis in the nation-wide Korean database. **Conclusions:** Older age, hypertension, and higher levels of C-reactive protein are useful factors for the prediction of aseptic encephalitis. (Korean J Clin Neurophysiol 2014;16:55-61)

Key Words: Blood-brain barrier, Meningitis, Encephalitis, Age, C-reactive protein

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Introduction

Infections of the central nervous system (CNS) are common in clinical practice. Viruses are the most common and important cause of CNS infections, although other organisms can cause CNS infections.¹ Viruses can cause either meningitis or encephalitis. Aseptic meningitis is a febrile illness that

is associated with clinical signs of meningeal irritation such as neck stiffness and the presence of Kernig's and Brudzinski's signs. In contrast, aseptic encephalitis is a febrile illness with evidence of brain parenchymal dysfunction that is manifested by an altered state of consciousness or by objective signs of neurologic dysfunctions, such as seizures, cranial nerve palsies, or paralysis.² Distinguishing between aseptic encephalitis and meningitis is important because the management and prognoses of these diseases are different.³ The mainstay of aseptic meningitis management is supportive care, whereas antiviral agents should be given intravenously as soon as possible when aseptic encephalitis is suspected.^{1,3} A delay in the initiation of treatment can result in increased morbidity and mortality in cases of aseptic encephalitis.⁴ Differentiation between aseptic encephalitis and meningitis is usually possible, but misdiagnoses of aseptic meningitis in the cases of encephalitis are sometimes made. For example, we examined some elderly patients who initially exhibited mild drowsiness, high fever, and lymphocytic pleocytosis in the cerebrospinal fluid (CSF). In these cases, it was difficult to determine the reason that these patients exhibited mild drowsiness, but this symptom might have been due to high-fever induced mild drowsiness in aseptic meningitis or to encephalitis-induced mental deterioration. Other markers which are helpful to determine aseptic meningitis or encephalitis may be needed.

It is unclear why some people suffer from aseptic meningitis, whereas others fall ill with aseptic encephalitis when infected with the same viral pathogens. One of the possible mechanisms could be that differences in the permeability of the blood-brain barrier might have play a critical role in determining whether aseptic meningitis or encephalitis develops.^{1,2,5} Viruses gain entrance to the body via several pathways, such as the respiratory or oral-to-intestinal route. Following entry into the body, viruses multiply locally or in secondary sites, which typically results in viremia.⁶ Viruses can invade the CNS through blood circulation.⁷ The CNS is sequestered from the systemic circulation by the blood-brain barrier.⁷ Aseptic encephalitis results from the parenchymal invasion of viruses that cross the blood-brain barrier, whereas restricted viral invasion in the meninges results in aseptic meningitis.^{1,2,5} Thus, the permeability of the blood-brain barrier might be an important mechanism in the development of aseptic encephalitis. There are some conditions, such as old

age, hypertension, diabetes, hormonal changes, and inflammation, that might result in increase in the permeability of blood-brain barrier.⁸⁻¹²

The aim of this study was to compare the demographic and laboratory profiles of patients with aseptic meningitis and encephalitis.

Methods

This study was approved by the Institutional Review Board at our institution. This case-control retrospective observational study was performed in a single tertiary hospital, which serves a population of approximately 400,000. From our hospital database, we recruited 155 patients with diagnoses of aseptic meningitis or encephalitis who were admitted to the Department of Neurology, Haeundae Paik Hospital in the time period from March 2010 to October 2012. We reviewed the medical records of these patients, and included the patients who had typical clinical histories and laboratory findings of aseptic meningitis or encephalitis.

The inclusion criteria of the patients with aseptic meningitis were the presence of clinical features, such as acute onset headache, fever, and signs of meningeal irritation, and positive CSF findings including the following: 1) lymphocytic pleocytosis, a normal or slightly elevated protein concentration, and a normal glucose concentration; 2) negative CSF staining, culture, or PCR for bacteria, mycobacteria and fungus; 3) negative for venereal disease based on a laboratory test for syphilis. We defined aseptic encephalitis based on clinical features that included acute onset fever and altered consciousness, CSF findings identical to those of aseptic meningitis discussed above, and abnormal findings that supported cortical lesions on one of the following: 1) focal or diffuse slow background activities on the electroencephalography (EEG); or 2) cortical abnormal signal changes on the computed tomography (CT) or magnetic resonance imaging (MRI).^{13,14} We excluded patients for the following: 1) bacterial, mycobacterial, fungal, parasitic, or para-meningeal infections; 2) malignancies including para-neoplastic syndrome; 3) autoimmune diseases including rheumatologic disease or autoimmune encephalitis with antibodies to cell surface or synaptic antigens; 4) medications that can cause meningeal inflammation; 5) inflammation of neighboring structures, e.g., caused by, brain

abscesses or epidural abscesses; or 6) encephalopathies with evidence of a vascular, malignant, metabolic, psychiatric, demyelinating, toxic, or traumatic etiologies.^{3,15}

All patients underwent tests that included PCR of the CSF/serum to identify of viral pathogens such as Epstein-Barr virus, varicella zoster virus, herpes simplex virus, cytomegalovirus, and enterovirus. The primary endpoint of this study was the diagnosis of aseptic encephalitis or meningitis. The demographic and laboratory differences were analyzed with age, sex, diabetes, hypertension, C-reactive protein (CRP) in the blood, white blood cells (WBCs) and protein in the cerebrospinal fluid (CSF), and glucose ratio (CSF/blood) as independent variables. If there were multiple CSF profile and CRP measurements, we analyzed the first CSF profiles and CRP measurements that were obtained on the day of admission.

We analyzed the categorical clinical variables using Fisher's exact test or the chi-square test, and used Student's t-test or the Mann-Whitney U-test for numerical variables. For the multivariate analyses, we dichotomized age as >49 years old or ≤49 years old, WBC as >95/mm³ or ≤95/mm³, and CRP levels as >5.81 mg/dL or ≤5.81 mg/dL. We performed multiple logistic regression analyses. The primary endpoint was the diagnosis of encephalitis, which was used as the dependent variable, and we included the variables that were significantly related to the primary endpoint in the univariate analyses as independent variables in the multivariate analysis. Additionally, we analyzed the nation-wide differences in age between the patients with aseptic meningitis and encephalitis in Korea from 2006 to 2011 using the databases of the Health Insur-

ance Review and Assessment Service of Korea (<http://www.hira.or.kr>). We use the International Classification of Disease (ICD)-10 code to define aseptic meningitis and encephalitis (A87 and A86, respectively). Additionally, we calculated the sensitivity, specificity, positive predictive value, and negative predictive value for the prediction of aseptic encephalitis. All statistical tests were performed, using MedCalc[®]. For all calculations, a *p*-values less than 0.05 were considered statistically significant.

Results

Of the 155 patients, 107 patients satisfied the inclusion and exclusion criteria for this study. Sixty five patients were men and 42 patients were women. The mean age was 35.8±15.3 years. Of the 107 patients, 11 patients had hypertension, and two patients had diabetes. The CSF study revealed that the median WBC count was 100/mm³ (95% CI 65-210/mm³, range 5-1,120/mm³), the median protein level was 55 mg/dL (95% CI 46-63 mg/dL, range 16-240 mg/dL), the mean glucose ratio (CSF/blood) was 0.56±0.089, and the median CRP level was 0.47 mg/dL (95% CI 0.3-1.0 mg/dL, range 0.01-28.6 mg/dL). Eight patients with viral pathogens were identified using PCR of the CSF. Among the aseptic meningitis patients, one patient had Epstein-Barr virus, one patient had varicella zoster virus, and five patients had herpes simplex virus. Among the aseptic encephalitis, one patient had herpes simplex virus. There were no significant differences in the viral pathogens between the aseptic meningitis and encephalitis patients.

Table 1. Comparisons of the demographic and laboratory profiles of the patients with aseptic meningitis and encephalitis

Parameter	Meningitis (n=89)	Encephalitis (n=18)	<i>p</i> -value
Men, n (%)	52 (58.4)	13 (72.2)	0.3049
Mean age, years (±SD)	32 (±12)	56 (±13)	<0.0001
Hypertension, n (%)	2 (2)	9 (50)	<0.0001
Diabetes, n (%)	1 (1)	1 (5)	0.3094
Median WBC*, mm ³ (95% CI)	130 (84-217)	36 (18-91)	0.0326
Median protein*, mg/dL (95% CI)	51 (44-62)	66 (44-96)	0.1882
Mean glucose ratio† (±SD)	0.56 (±0.089)	0.57 (±0.114)	0.6555
Median CRP‡, mg/dL (95% CI)	0.43 (±3.17)	1.28 (8.00)	0.0474

*Cerebrospinal fluid; †Cerebrospinal fluid/blood; ‡Blood.

WBC; white blood cell, CRP; C-reactive protein, CI; confidence interval.

Table 2. Results of multivariate analysis of the variables of the patients with aseptic meningitis and encephalitis

Independent variable	Adjusted odds ratio	95% confidence interval	p-value
Age (>49 years)	27	4.6-163.9	0.0003
Hypertension	15	1.7-132.5	0.0153
WBC* (<95/mm ³)	4	0.5-23.7	0.1925
CRP† (>5.81 mg/dL)	15	1.1-92.1	0.0201

*Cerebrospinal fluid; †Blood.
WBC; white blood cell, CRP; C-reactive protein.

Table 3. Sensitivities, specificities, positive predictive values, and negative predictive values in the prediction of aseptic encephalitis by variable

Independent variable	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Age (>49 years)	0.78	0.91	0.64	0.95
Hypertension	0.50	0.98	0.82	0.91
CRP* (>5.81 mg/dL)	0.30	0.91	0.43	0.87

*Blood.
CRP; C-reactive protein.

Amongst the 107 patients, 89 patients were diagnosed with aseptic meningitis and 18 patients had encephalitis. Table 1 shows a comparison of the demographic and laboratory profiles of the patients with aseptic meningitis and encephalitis. The age of onset of the patients with encephalitis was significantly older than that of the patients with meningitis (56 years vs. 31 years, $p < 0.0001$ by Student's *t*-test). Of the 18 patients with encephalitis, nine patients had hypertension, whereas two patients with meningitis had hypertension (9/18 vs. 2/89, $p < 0.0001$ by Fisher's exact test). Moreover, the WBC counts in the CSF and the CRP levels in the blood were significantly different between the patients with encephalitis and those with meningitis (134/mm³ vs. 200/mm³, $p = 0.0326$ by Mann-Whitney U-test; 5.45 mg/dL vs. 1.88 mg/dL, $p = 0.0474$ by Mann-Whitney U-test, respectively).

Multiple logistic regression analysis revealed older age (>49 years), hypertension, and a high CRP level (>5.81 mg/dL) were independent and significant variables in the prediction of aseptic encephalitis (Table 2). These variables had relatively low sensitivities and positive predictive values, but they had high specificities and negative predictive values. Among these variables, age of onset (>49 years) was more strongly predictive of having encephalitis than were the other clinical variables. The specificity and negative predictive value of age of onset were 0.91 and 0.95, respectively (Table 3).

In the databases of the Health Insurance Review and Assessment Service, the approximate number of patients with aseptic meningitis was 10,000 per year and the number of aseptic encephalitis patients was approximately 500 per year from 2006 to 2011 in Korea. Consistently, there were significant nation-wide differences in age (>49 years) between the patients with aseptic meningitis and those with encephalitis in Korea for each of the years from 2006 to 2011 (Suppl. Table 1). The risk of having aseptic encephalitis might increase as much as ten-fold more than that for aseptic meningitis with older age (>49 years; OR=10, 95% CI: 9.6-11.4).

Discussion

Although the clinical manifestations of aseptic encephalitis are different from those of aseptic meningitis, the initial symptoms of patients with aseptic encephalitis can be non-specific. Brain images, such as those from CT and MRI, that are obtained early in the course of aseptic encephalitis are often normal or subtly abnormal.^{16,17} Although EEG reveals specific features that can provide clues in a limited proportion of cases, EEG is typically nonspecific.^{16,17} Our study revealed that there were also no differences in the CSF profiles (including WBC counts, protein levels, glucose ratios) between the aseptic meningitis and encephalitis patients. Thus, it

might be difficult to distinguish aseptic encephalitis from aseptic meningitis with these diagnostic tools. However, our study suggests that age of onset (>49 years) and a high CRP level (>5.81 mg/dL) were significant variables in the prediction of aseptic encephalitis as opposed to meningitis. Thus, our results are useful for the differentiation of aseptic encephalitis from meningitis in clinical practice.

The blood-brain barrier is a structural and functional barrier that regulates the passage of blood-borne substances and cells into the brain and thus maintains the homeostasis of the neural microenvironment.¹⁸ The permeability of the blood-brain barrier increases with normal ageing, and this fact might have contributed to the viral crossing of the blood-brain barrier and the subsequent development of aseptic encephalitis.⁸ Our study confirmed that the age of onset of the patients with aseptic encephalitis was older than that for the aseptic meningitis patients. In our study, only 17% (3/18) of the patients who had aseptic encephalitis were younger than 49 years old, and all of three of these patients were heavy alcoholics. There is also some evidence that alcohol abuse can impair the permeability of the blood-brain barrier via modifications of the tight junctions of endothelial cells.¹⁹ After the viruses cross the blood-brain barrier, they can cause brain damage via inflammation, and direct infection.²⁰⁻²² The viruses trigger an anti-viral immune response, which initiates an inflammatory cascade to control viral replication and dissemination.²⁰⁻²² The extent of the pro-inflammatory response in the CNS and the timing of the release of pro-inflammatory cytokines, such as tumor necrosis factor- α and interleukin-6, can lead to neuronal excitability and injury.²⁰⁻²²

We performed tests that included PCR to identify the viral pathogens, and we found no significant differences in the viral pathogens of the meningitis and encephalitis patients. Additionally, although viruses that cause meningitis and encephalitis are not identical, many viruses, such as enterovirus, Epstein-Barr virus, varicella zoster virus, herpes simplex virus, and arthropod-borne virus, can cause either meningitis or encephalitis.¹⁴ Furthermore, the CSF profiles (including WBC counts, protein levels, and glucose ratios) were not different between the two groups in our study. These findings might be explained by the fact that the viral pathogens responsible for meningitis and encephalitis were not different in our study.

Because this study was conducted in a single tertiary hospi-

tal, our findings might have been influenced by selection bias. Thus, we also analyzed a nation-wide database to confirm that our findings were not limited to our hospital. The Health Insurance Review and Assessment Service is a public institution that manages health insurance in Korea. We analyzed the data regarding CNS infections in Korea from 2006 to 2011 using the databases of the Health Insurance Review and Assessment Service. Although we used only the ICD-10 codes to determine the nation-wide incidences of aseptic meningitis and encephalitis rather than performing a prospective epidemiological study, we found a similar statistically significant difference in the age of onset (>49 years) between from 2006 to 2011. These Health Insurance Review and Assessment Service data support the notion that the results of our study are not limited to our hospital. However, in contrast to our results, a previous study revealed that aseptic encephalitis occurred more frequently in young adults despite of no direct comparison in age of onset between aseptic meningitis and encephalitis patients.²³ This discrepancy may be caused by different objects with variable viral pathogens. To confirm our results, identification of the viral pathogens may be needed.

Our results are in accordance with reports that acute and chronic hypertension also increase the permeability of the blood-brain barrier due to defects in the synthesis or release of nitric oxide.⁹ The patients with aseptic encephalitis were consistently more hypertensive than were those with meningitis in our study. Furthermore, there have been reports that the blood-brain barrier becomes more permeable in inflammatory conditions.^{11,12} There is also a report that stated that excess CRP itself impairs the function of the blood-brain barrier.²⁴ In our study, the CRP levels of the patients with aseptic encephalitis were higher than those of the patients with aseptic meningitis. Our findings suggest that CRP is not only helpful in distinguishing between bacterial and aseptic meningitis but is also helpful in distinguishing aseptic encephalitis and meningitis.²⁵

This study has limitations. First, this was an observational study rather than a prospective epidemiological study. Second, the sample size was relatively small, particularly in terms of the number of patients with aseptic encephalitis. Third, because we used only the ICD-10 codes to determine the nation-wide incidences of aseptic meningitis and encephalitis, the diagnoses might be not accurate. Multicenter prospective epi-

demioleological studies might be required. Fourth, the terms aseptic meningitis and encephalitis can be used broadly and include all types of meningitis and encephalitis with negative CSF bacterial cultures.^{1,3} Although the etiologic agents are variable and include fungal and parasitic infections, drugs, systemic diseases, neoplastic disorders, and inflammation of neighboring structures, viral infections are the most common cause of aseptic meningitis and encephalitis.^{3,26} Additionally, we excluded patients who had other causes of meningitis or encephalitis. Thus, although we identified the exact viral pathogens in only eight patients with PCR, we assumed that the causes of aseptic meningitis and encephalitis were viruses in our study. Fifth, PCR methods have improved the detection of viral pathogens, and the results of PCR methods are available more quickly and are more sensitive than those of viral cultures.¹⁴ The sensitivity of PCR ranges from 40 to 100 percent in patients with aseptic meningitis and encephalitis.^{14,15} However, in our study, the detection rates of viral pathogen using PCR were lower than the widely known identification rates. A plausible explanation for this discrepancy is that the CSF for the PCR tests was collected at an inappropriate time during the illness. There have been several reports of initially negative CSF PCR tests that were obtained early (≤ 72 h) following the onset of symptom.^{1,14} In this study, we performed lumbar punctures as early as possible to determine the appropriate diagnosis and treatment, and the majority of the CSF samples from our patients were examined within 24 h of the onset. To identify viral pathogens, repeated lumbar punctures to obtain CSF for PCR tests for three days after onset might be required.^{1,14} Sixth, we did not find any pathologic evidence that supported our hypothesis of the existence of a difference in blood-brain barrier permeability between the aseptic meningitis and encephalitis patients.

In conclusion, we demonstrated that age of onset (>49 years), hypertension, and higher CRP levels (>5.81 mg/dL) were independent and significant variables in the prediction of aseptic encephalitis. These variables had high specificities and negative predictive values; thus, clinicians should be cautious when a diagnosis of aseptic meningitis is suspected in patients with these risk factors.

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