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Hippocampal sclerosis and encephalomalacia as prognostic factors of tuberculous meningitis-related and herpes simplex encephalitis-related epilepsy

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ABSTRACT

Background: Tuberculous meningitis (TBM) and herpes simplex encephalitis (HSE) are common neurological diseases involving the brain parenchyma, and both can result in chronic epilepsy. Here, we identified possible variables affecting the prognosis of central nervous system (CNS) infection-related epilepsy.

Methods: The clinical seizure characteristics and demographic data of 20 TBM- and 55 HSE-related epilepsy patients were compared. Statistically significant prognostic variables were identified using multiple regression analysis.

Results: Sex, age at infection, age at epilepsy onset, presence of seizures at the time of infection, latency period, and seizure characteristics between two groups were similar except for the pattern of brain lesions observed on the MRI and their overall prognosis. Patients with hippocampal sclerosis (HS) only comprised 30% and 52.7% of the TBM and HSE groups, respectively. Encephalomalacia had a positive effect in the HSE group while HS had a negative effect in this group, but no significant effects were found in the TBM group. Through a multiple regression analysis with a correction for group effects, HS was associated with a poor prognosis. However, encephalomalacia was concomitantly associated with a good prognosis. In addition, a short latency period, with a one-year interval, and being male were both associated with a good prognosis, while the age at the onset of epilepsy was associated with a poor prognosis.

Conclusions: This study suggests that HS and encephalomalacia could have mutual but contradictory effects on the prognosis of CNS infection-related epilepsy.

1. Introduction

Any central nervous system (CNS) infection affecting the brain parenchyma can result in epilepsy as a chronic sequela as well as acute seizures at the time of infection. Tuberculous meningitis (TBM) is the most frequent and severe manifestation of CNS involvement during tuberculosis, and herpes type 1 encephalitis is the most common cause of sporadic viral encephalitis worldwide. An epidemiologic study on all types of encephalitis based on 20-year follow-up reported chronic epilepsy in 22% of patients who experienced seizures during acute encephalitis.[1] Chronic epilepsy as a sequela of CNS infection in TBM occurs in more than 20% of cases.[2,3] In cases of herpes simplex encephalitis (HSE), 16–24% of survivors are known to develop epilepsy.[1,4]

CNS infection is one of the multi-factorial aetiologies of epilepsy; however, CNS infection-related epilepsy has not been studied in detail, especially in terms of prognosis and prognostic factors. Importantly, previous studies have predominantly examined patients with CNS infection,[5] not patients with CNS infection-related epilepsy. In one study investigating catastrophic post-encephalitic epilepsy,[6] the study population was based on surgical candidates with intractable epilepsy.

This study focused on patients with TBM- and HSE-related epilepsy. Each patient presented with distinct clinical manifestations due to the different underlying pathophysiologies, which result in lesions on the brain parenchyma in specific locations depending on the aetiology. These lesions appeared to give rise to prognostic differences, which prompted us to compare the demographic data and clinical seizure characteristics of the two groups. Interestingly, the pattern of brain lesions detected using MRI and the overall prognosis were statistically significant variables. The distinct patterns of brain lesions underlying the different inflammatory processes are thought to be related to prognosis in CNS infection-related epilepsy.

Herpes simplex virus type 1 is known to have a predilection for limbic structures,[7] including the temporal lobe. The frequently observed lesions in this area during acute inflammatory processes result in focal/diffuse atrophy or encephalomalacia. Hippocampal

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sclerosis (HS) is common in HSE and can also be found in TBM. Studies using experimental models have suggested a common final pathway for seizure generation and propagation in multiple conditions with various causes.[2] We hypothesised that CNS inflammatory processes may work via a common process even though the underlying pathogen is different and that the resulting brain lesions may give rise to different prognoses.

Here, we identified possible variables affecting the prognosis of CNS infection-related epilepsy. The comparison of the clinical profiles between the patients with TBM- and HSE-related epilepsy focused on the brain lesions in each group. The clinical variables affecting prognosis, especially encephalomalacia and HS, were also statistically analysed. These results will extend our understanding of CNS infection-related epilepsy.

2. Methods

We retrospectively studied 55 patients with HSE-related epilepsy and 20 patients with TBM-related epilepsy who were evaluated between March 1994 and February 2010 at the Yonsei University Medical Centre. A positive polymerase chain reaction for herpes simplex virus in the cerebrospinal fluid (CSF), mental changes concomitant with EEG, and typical CSF profiles were compatible with a diagnosis of HSE. The diagnosis of TBM was based on positive culture of acid-fast bacilli (AFB) in the CSF, which was found in 13 patients. A CSF profile with elevated adenosine deaminase and accompanying evidence of tuberculosis in the body were also considered in the diagnosis of TBM in AFB-negative patients. Referred patients were included with documented CSF profiles and positive serological results. CNS infection-related demographic data, such as sex, age at infection, age at the onset of epilepsy, presence of seizures at the time of infection, and latency period from the time of infection to the onset of epilepsy, were compared between the two groups. The clinical characteristics of temporal lobe epilepsy (TLE) such as aura or automatism were recorded. The general characteristics of the seizures, such as partial seizure without secondary generalized tonic–clonic (GTC) seizure, clustering nature, and nocturnal dominance, were analysed. Nocturnal dominance was defined as more than 90% of habitual seizures occurring during sleep.

The MRI findings were reviewed by a neuroradiologist and the corresponding author, both of whom were blinded to the diagnosis, and classified as follows: HS only, HS with encephalomalacia, encephalomalacia only, and normal. Encephalomalacia cases were further divided into unilobar and multilobar involvement depending on the extent of malatic change. Hemiatrophy or diffuse atrophy of the cortex was regarded as multilobar involvement. The minimal follow-up duration for analysis of prognosis was two years. The prognosis of patients who had undergone epilepsy surgery (three in the TBM group and nine in the HSE group) was based on a 12-month follow-up before the surgery. The prognosis was categorized depending on the reduction in the frequency of seizures: Seizure-free or rare aura only; more than a 50% reduction; less than a 50% reduction; and no change or aggravation. The prognosis was also divided into two groups: patients with no seizures or rare aura and more than a 50% reduction were grouped as ''good'' prognosis, and patients with less than a 50% reduction and no change or aggravation were grouped as ''poor'' prognosis. A statistical comparison of the clinical profiles between the TBM and HSE groups was conducted using the Chi-square test, and variables with prognostic significance were then analysed using simple logistic regression. The latter criteria for the prognosis were used for statistical analysis. Multiple logistic regression tests, depending on the significant covariate, were conducted to identify prognostic factors in each group and in all patients, regardless of disease type. SAS software (version 9.1.3) was used for the statistical analyses.

Table 1
Demographic data and clinical profiles of the patients with epilepsy.

Clinical variable	TBM group ($n=20$)	HSE group ($n=55$)	p value[b,c]
Demographic data			
Sex (M:F)	10:10	34:21	NS/0.03
Mean age of infection ± SD (range), years.	10.0 ± 12.2 (1–40)	15.4 ± 18.8 (0.1–68)	NS/NS
Latent period ± SD (range), years.	5.3 ± 6.5 (0–22)	5.0 ± 6.9 (0–34)	NS/0.01
Mean age at epilepsy onset ± SD (range), years.	15.2 ± 11.2 (1–40)	20.3 ± 17.6 (1–69)	NS/0.08
Presence of seizures at time of infection (%)	7/12[a] (58.3)	39/47[a] (83%)	NS/NS
F/U duration ± SD (range), m.	83.8 ± 54.2 (24–192)	109.5 ± 79.6 (24–204)	
Clinical characteristics of seizure, n (%)			
Clinical feature of TLE	12 (60)	35 (63.6)	NS/NS
Aura/limbic aura	16 (80)/10 (50)	34 (61.8)/14 925.5)	NS/NS
Automatism	11 (55)	33 (60)	NS/NS
Secondary GTC	15 (75)	40 (72.7)	NS/NS
Clustering nature	1 (5)	9 (16.4)	NS/NS
Nocturnal dominancy	5 (25)	5 (9.1)	NS/NS
Pattern of lesion on brain MRI, n (%)			
HS only	6 (30) (3 bil.)	29 (52.7) (10 bil.)	
Encephalomalacia only	5 (25)	6 (10.0)	
Unilobar/multilobar involvement	2/3	3/3	
HS with encephalomalacia	7 (35)	20 (36.4)	
Unilobar/multilobar involvement	3/4	6/14	
Normal	2 (10)	0	
Overall prognosis, n (%)			
Good prognosis			
Seizure free or aura only	6 (30)	13 (23.6)	
More than 50% reduction in seizure frequency	6 (30)	4 (7.3)	
Poor prognosis			
Less than 50% reduction in seizure frequency	4 (20)	17 (30.9)	
No change or aggravation	4 (20)	21 (38.2)	

NS, nonspecific significance; F/U, follow up; TLE, temporal lobe epilepsy; GTC, generalized tonic–clonic seizure; bil., bilateral.
[a] Presence of seizure at the time of infection was unclear in 8 cases in TBM group and in 8 cases in HES group.
[b] p- value of Chi-square test between TBM and HSE.
[c] A simple logistic regression analysis was used to reveal prognostic factors among all patients.

3. Results

A Chi-square analysis of the demographic and clinical seizure characteristics of the subjects did not identify any significantly different variables between the TBM and HSE groups even though some gross differences were apparent (Table 1). The mean age of infection was 10.0 ± 12.2 years in the TBM group and 15.4 ± 18.8 years in the HSE group. The mean age at the onset of epilepsy was 15.2 ± 11.2 years in the TBM group and 20.3 ± 17.6 years in the HSE group, with a latency period of 5.3 ± 6.5 years and 5.0 ± 6.9 years, respectively. Seizures were present at the time of infection in 58.3% of the TBM group and 83% of the HSE group. The presence of seizures at the time of infection was not clearly defined in eight cases in the TBM group and in eight cases in the HSE group. The clinical features of TLE, including aura and automatism, secondary generalized TCG, a clustering nature, and nocturnal dominance, did not differ between the two groups (Table 1).

Both the prognosis and the brain lesion pattern were statistically significant between the TBM and HSE groups ($p = 0.03$ and 0.02, respectively; Chi-square). Patients with HS only comprised 30% and 52.7% of the TBM and HSE groups, respectively, and patients with encephalomalacia only comprised 25% and 10% of the TBM and HSE groups, respectively. Multilobar involvement in the encephalomalacia was observed in 58.3% (7/12) and 65.4% (17/26) of the TBM and HSE groups, respectively. Four cases of tuberculoma and two cases of basal ganglia infarction were noted in the TBM group, and five cases of hemiatrophy and two cases of diffuse atrophy were regarded as multilobar involvement in the HSE group.

When the prognosis was defined as "good" or "poor", 60% of the TBM and 30.9% of the HSE patients fell into the good prognosis group, and 40% of the TBM and 69.1% of the HSE patients fell into the poor prognosis group.

A significant correlation between the prognosis and the pattern of brain lesions was observed in the HSE group, not in the TBM group. The statistical significance was greater when all patients were analysed irrespective of group (Table 2). These results suggest that HS and encephalomalacia are the main factors affecting prognosis. While the prognoses based on encephalomalacia irrespective of HS or the prognoses based on HS irrespective of encephalomalacia were not significant for each group, a simple logistic regression analysis determined that encephalomalacia ($p = 0.02$) showed more prognostic significance than HS ($p = 0.057$; Tables 3 and 4). These results demonstrate that the brain lesion pattern could have prognostic value, regardless of the group.

Using a simple logistic analysis, sex, latency period, and age at the onset of epilepsy were also determined to be covariates with prognostic significance (Table 1) in which multicollinearity was verified. A multiple logistic regression analysis was conducted for each group and for both groups combined. In the HSE group, encephalomalacia wad correlated with a positive prognosis ($p = 0.031$), while HS was correlated with a negative prognosis ($p = 0.046$). No significant effects were observed in the TBM group. When encephalomalacia and HS were considered together, encephalomalacia was associated with a positive prognosis (odds ratio = 4.133; 95% CI, 1.144–14.928; $p = 0.03$), but HS was associated with a negative prognosis (odds ratio = 0.231; 95% CI, 0.044–1.211; $p = 0.08$). Among the statistically significant covariates, being male showed a positive prognostic effect compared to being female, and a shorter latency period with a one-year interval was also associated with a good prognosis (Table 5). However, age at the onset of epilepsy was associated with a poor prognosis.

Table 2
Prognosis depending on the pattern of MRI lesions.

	Good Pn.[a]	Poor Pn.[b]	p value[c]	p value[d]
TBM group				
HS only ($n = 6$)	1	5		
Encephalomalacia only ($n = 5$)	4	1		
HS with encephalomalacia ($n = 7$)	5	2	NS	
Normal ($n = 2$)	2	0		0.02
HSE group				
HS only ($n = 29$)	6	23		
Encephalomalacia only ($n = 6$)	3	3		
HS with encephalomalacia ($n = 20$)	8	12	0.03	
Normal ($n = 0$)	0	0		

Pn, prognosis; NS, nonspecific significance.
[a] Patients with no seizures or aura only and more than a 50% reduction in seizure frequency.
[b] Patients with less than a 50% reduction in seizure frequency and no change or aggravation.
[c] Determined using a Chi-square test.
[d] Determined using a simple logistic regression analysis.

Table 3
Prognosis depending on encephalomalacia irrespective of HS.

	Good Pn.[a]	Poor Pn.[b]	p value[c]	p value[d]
TBM group			NS	
With encephalomalacia ($n = 12$)	9	3		
Without encephalomalacia ($n = 8$)	3	5		
HSE group			NS	0.02
With encephalomalacia ($n = 26$)	11	15		
Without encephalomalacia ($n = 29$)	6	23		

Pn, prognosis; NS, nonspecific significance.
[a] Patients with no seizures or aura only and more than a 50% reduction in seizure frequency.
[b] Patients with less than a 50% reduction in seizure frequency and no change or aggravation.
[c] Determined using a Chi-square test.
[d] Determined using a simple logistic regression analysis.

Table 4
Prognosis depending on HS irrespective of encephalomalacia.

	Good Pn.[a]	Poor Pn.[b]	p value[c]	p value[d]
TBM group			NS	
With HS ($n = 13$)	6	7		
Without HS ($n = 7$)	6	1		
HSE group			NS	0.05
With HS ($n = 49$)	14	35		
Without HS ($n = 6$)	3	3		

Pn, prognosis; NS, nonspecific significance.
[a] Patients with no seizures or aura only and more than a 50% reduction in seizure frequency.
[b] Patients with less than a 50% reduction in seizure frequency and no change or aggravation.
[c] Determined using a Chi-square test.
[d] Determined using a simple logistic regression analysis.

4. Discussion

While transient and strictly controlled inflammation in the brain is an adaptive response, chronic, inappropriately controlled inflammation in the brain can become detrimental to neurons and

Table 5
Result of the logistic multiple regression analysis when both groups were combined to correct for the effect of group.

Significant covariate	Estimate[a]	p value	Odds ratio	95% confidence interval
Encephalomalacia	1.4191	0.0303	4.133	1.144–14.928
HS	−1.4659	0.0831	0.231	0.044–1.211
Sex (male)	1.5912	0.0218	4.910	1.261–19.114
Latency period	0.0990	0.0347	1.104	1.007–1.210
Age at the onset of epilepsy	−0.0289	0.2250	1.104	1.007–1.210

[a] Compatible with regression coefficient.

is one of the various maladaptive changes in the CNS induced by epileptic activities or by pre-existing brain pathologies.[8] A recent study examining active neuroinflammation and marked cellular injury in the pathology of paediatric epilepsy surgery has suggested a common pathogenic role or consequence in childhood epilepsy with diverse aetiologies.[9] Although the pathophysiologic basis of chronic epilepsy following CNS infection is not well known, reactive gliosis after neuronal damage from changes in the local cellular and biochemical environmental is thought to be related to seizure induction. Studies using experimental models have suggested the likelihood of a common final pathway for seizure generation and propagation in multiple conditions with various causes.[2]

Approximately 2% of tuberculosis cases develop TBM,[10] and parenchymal invasion or tuberculoma formation can result in chronic epilepsy with a latency period. Post-encephalitic encephalomalacia, including HS in limbic structures, the preferred area in herpes simplex virus type 1 infection, is commonly related to symptomatic epilepsy.

This study focused on the clinical variables affecting the prognosis of CNS infection-related epilepsy. A comparison of the demographic data and the clinical seizure characteristics of the subjects with TBM and HSE showed no significant difference between the groups, with the exception of the overall prognosis and the brain lesion pattern apparent following MRI. Interestingly, the mean latency period was almost the same in the TBM and HSE groups, with a 5.3-year and 5.0-year latency period, respectively. The latency period of the TBM group was much shorter than both the 8.5 years observed in patients with meningitis of unknown cause[11,12] and the 15 years or more in patients with brain abscesses.[12,13] The latency period in our HSE group was similar to the 4.5 years reported by Lancman and Morris.[11] However, the latency period following of catastrophic post-encephalitic epilepsy was 0.8 years, during which the majority of patients were referred for presurgical evaluation. Furthermore, 32 of the 42 patients showed no latency period from the initial insult to the onset of recurrent seizures.[6] The most important predictive factor for the development of epilepsy has been reported to be status epilepticus during encephalitis,[14] and acute seizure at the time of infection has been proposed to be another possible risk factor of later epilepsy. The overall incidence of acute symptomatic seizure following CNS infection regardless of the pathogen has been reported to be 23%.[1,15] The incidence of acute seizures at the time of acute CNS infection was highest in HSE with an incidence of 62%[16] or 67%[17] and in TBM with an incidence of 16.3–31.5%.[18,19] While our results are higher than those previously reported, the reason for this difference is that all of the subjects in our study were epilepsy patients, and, in contrast to the above mentioned studies, all were patients with CNS infection.

Similar to the demographic data, the clinical seizure characteristics, such as the characteristics of TLE, secondary GTC, a clustering nature, and nocturnal dominance, were not statistically different between the two groups. While TBM and HSE had clearly different symptomatic presentations and clinical progress at the acute stage due to different underlying pathophysiologies, the lack of a statistical difference in the epilepsy-related variables between the two groups suggests that there may be a common pathway for epileptogenesis that may be related to an inflammatory process during CNS infection, further supporting the aforementioned hypotheses.[2,9] Involvement of the mesial temporal structure during CNS infection is common and has been reported in 64.3% of patients who underwent epilepsy surgery following CNS infection.[11] In one study, 13 of the 17 patients with status epilepticus or repetitive seizure during the acute phase of the encephalitis were confirmed to have HS.[4] Our data in CNS infection-related epilepsy showed that the involvement of HS alone was 30% and 52.7% in the TBM and HSE groups, respectively, and in combination with encephalomalacia was 65% and 89.1%, respectively. The pattern of brain lesions detected using MRI was different between two groups, but the pattern of lobar encephalomalacia involvement was not appreciably different between the two groups. In terms of overall prognosis, while the difference between the two groups was clear, the prognosis depending on the pattern of brain lesions was only statistically significant in the HSE group. The analysis irrespective of group demonstrated that the pattern of brain lesions may clearly affect the prognosis of these two groups.

The statistical analysis showed that encephalomalacia, irrespective of the presence of HS, did not significantly affect prognosis in either group. Additionally, HS, irrespective of the presence of encephalomalacia, did not affect the prognosis in either group. However, each factor (HS and encephalomalacia) was an independent, significant prognostic factor when corrected for the group effect. These results suggest that HS and encephalomalacia could function as prognostic factors rather than contributing to the underlying aetiology of CNS infection-related epilepsy. It also supports the hypothesis that there may be a common pathway for epileptogenesis related to inflammatory processes resulting from CNS infections.

In addition to HS and encephalomalacia, being male, latency period, and age at the onset of epilepsy were confirmed as covariates related to prognosis. A multiple regression analysis examining sex, latency period, and age at the onset of epilepsy on each group showed that HS and encephalomalacia could function as negative and positive prognostic factors in the HSE group, respectively, but were not significant factors in the TBM group. When the group effect was statistically corrected for, HS had a negative prognostic effect while encephalomalacia was a positive prognostic factor. Similarly, while the other covariates could not function as prognostic factors when groups were analysed separately, following the correction for the group effect, being male was found to be a positive prognostic factor. Furthermore, a shorter latency period was a positive prognostic factor while age at the onset of epilepsy was a negative prognostic factor.

5. Conclusions

The demographic data and clinical epilepsy characteristics of subjects with TBM- and HSE-related epilepsy were similar except for the pattern of brain lesions and overall prognosis. HS and encephalomalacia may function more as prognostic factors rather than being simply related to the underlying aetiology of CNS infection-related epilepsy. These results suggest that there may be a common pathway for epileptogenesis related to inflammatory processes resulting from CNS infections.

Sex, latency period, and age at the onset of epilepsy were also independent prognostic factors when the data were corrected for the group effect. As determined using multiple regression analysis, encephalomalacia had a positive effect and HS had a negative effect in the HSE group, but no significant effects were found in the TBM group. When corrected for the group effect, HS was associated with a poor prognosis while encephalomalacia was associated with a good prognosis. Along with HS and encephalomalacia, being male and having a shorter latency period were both associated with a good prognosis, but age at the onset of epilepsy was negatively associated with prognosis.

This study suggests that HS and encephalomalacia could have mutual but contradictory effects on the prognosis of CNS infection-related epilepsy. Additional, more extensive studies of CNS infection-related epilepsy with different underlying aetiologies are needed to further clarify this situation.

Conflict of interest

None declared.

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