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Central Nervous System Infection-Related Isolated Hippocampal Atrophy as Another Subtype of Medial Temporal Lobe Epilepsy with Hippocampal Atrophy: A Comparison to Conventional Medial Temporal Lobe Epilepsy with Hippocampal Atrophy

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Background and Purpose Hippocampal atrophy (HA) resulting from a central nervous system (CNS) infection might be a relevant lesion responsible for the clinical characteristics of medial temporal lobe epilepsy.

Methods The clinical characteristics of 54 patients with CNS infection-related medial temporal lobe epilepsy (MTLE) with isolated HA (CNS infection group) and 155 patients with conventional MTLE with HA (conventional group) were compared retrospectively. CNS infection alone and bilateral involvement of the HA were analyzed as prognostic factors, in addition to the detailed clinical characteristics, such as limbic aura and the presence and proportion of each type of automatism, between the two groups, and both medical and surgical prognoses were separately considered. A logistic regression analysis was performed.

Results A statistical analysis including all clinical factors, including CNS infection with bilateral HA, did not reveal significant differences between the two groups. An analysis comparing the prognosis of the two groups based on good or poor prognosis among patients who received medical treatment and good or poor outcomes among patients who received surgical treatment did not produce significant differences.

Conclusions In addition to bilateral HA, CNS infection alone was not a poor prognostic factor for the CNS infection-related epilepsy with HA group compared with the conventional MTLE with HA group. Based on these negative results, HA is a plausible and relevant lesion with similar clinical characteristics to HA in patients with conventional MTLE. Therefore, CNS infection-related MTLE with isolated HA might represent another subtype of MTLE with HA with a different etiology.

Key Words central nervous system infection, medial temporal lobe epilepsy, hippocampal atrophy, brain MRI.

INTRODUCTION

Medial temporal lobe epilepsy (MTLE) is a discrete syndrome or group of clearly distinct syndromes[1] with different clinicopathological and electrophysiological characteristics. When combined with hippocampal atrophy (HA) as the most important hallmark of MTLE, MTLE-HA is recognized as a distinct syndrome, representing a subtype of MTLE.[2] The great majority of these patients have a history of complicated febrile convulsions or other initial precipitating injury.[3,4] Febrile seizure (FS) is associated with TLE in approximately 37–66% of

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patients.[5-8] Based on accumulating evidence from MRI and pathological studies, FS is the most plausible cause of HA.[2,9,10] Thus, FS may predispose affected individuals with MTLE to HA. Several cytokines and proinflammatory signaling pathways play roles in both experimental models and clinical cases of epilepsy.[11-13] Fever involves inflammatory mediators such as the cytokines tumor necrosis factor-α and interleukin-1β[14,15-17] that promote neuronal hyperexcitability,[18] and proinflammatory cytokines are implicated in seizure disorders.[19-21] A pathological study reported the overexpression of nuclear factor kappa-light-chain-enhancer of activated B cells, a transcription factor, during acute inflammation in patients with temporal lobe epilepsy,[22] suggesting that inflammation might be involved in the underlying mechanism of epilepsy.

However, the cause-and-effect relationship remains controversial. HA occurs in a large percentage of patients (approximately 70%) with MTLE without evidence of FS,[18] and population-based prospective studies of FS have not provided evidence of any association.[21,23-25] To date, many patients with MTLE have been reported to have a history of FS, whereas some patients with MTLE-HA do not. These observations have sparked a debate concerning the etiology of HA,[18] which does not appear to be caused by a single etiological factor.

A variety of other early precipitating insults, such as trauma and infection, are also associated with MTLE.[25,26] Brain infections are implicated in the etiology of at least 7% of all cases of epilepsy.[27-29] According to some studies,[18,22,30-33] immune and inflammatory reactions occurring at birth or during a patient's lifetime might initiate a cascade of chronic inflammatory events in the central nervous (CNS) that contribute to late-onset epilepsy. An insult caused by CNS inflammation might damage any structure of the brain, and the temporal lobe, including the medial temporal structure, is often identified as a predisposing lesion in patients with CNS infection-related epilepsy,[34] resulting in uncommon isolated HA.

HA in the brain is a well-known clinically and pathophysiologically relevant lesion observed in patients with conventional MTLE. The involved networks of epileptogenesis after brain insult may differ due to varying underlying causes, uncommonly resulting in HA. However, HA resulting from common probable epileptogenesis after febrile insults may share or reveal the clinical characteristics of epilepsy. If the clinical characteristics of CNS infection-related HA are not different from those of MTLE-HA without a history of CNS infection as conventional MTLE, then CNS infection-related HA might represent a subset of MTLE with a different etiology.

No study conducted to date has sufficiently answered this question. Therefore, we compared the clinical significance of HA between patients with CNS infection-related epilepsy and conventional MTLE by analyzing the clinical characteristics and the differences in medical and surgical prognoses between the two groups.

METHODS

Patient grouping

Two hundred nine patients with MTLE with HA were enrolled through a retrospective review of medical records from March 1994 to September 2017. MTLE with HA was defined as follows: 1) a medical history compatible with history of complicated febrile convulsion or other initial precipitating injury, 2) ictal semiology compatible with a limbic nature, 3) ictal or interictal epileptiform discharge originating from the temporal lobe, and 4) HA on an MRI scan (refer to the detailed description of the criteria for MRI). Fifty-four of the 209 patients had a history of CNS infection, resulting in MTLE exhibiting isolated HA, and these patients were allocated to the CNS infection group. Individuals presenting a simple febrile illness without a mental change or documentation of cerebrospinal fluid profiles were not included. Thirty-seven of the 54 patients in the CNS infection group had received medical treatment from the corresponding author, and the remaining 17 patients, who were referred, met the aforementioned inclusion criteria. Twenty-nine patients were confirmed to be diagnosed with herpes simplex encephalitis, and 5 patients were diagnosed with tuberculous meningitis. The diagnoses of the other patients were ascertained by clear medical documentation of encephalitis, although the etiologies were unclear. One hundred fifty-five patients with MTLE with isolated HA were enrolled. None of these patients had a medical history of the aforementioned CNS infections. These patients were designated the conventional MTLE group. The history of FS was documented in detail in terms of the nature of the simple or complex febrile event. The presence of seizure at the time of CNS infection, which was differentiated from FS, was documented. Interictal epileptiform discharges from medial temporal areas were confirmed in an electroencephalogram with additional nasopharyngeal electrodes, which was regularly performed every 2 years in most all patients. Seventeen patients (31.5%) in the CNS infection group and 62 (40%) patients in the conventional group underwent tailored temporal lobectomy with amygdalohippocampectomy. The epileptic focus in the patients who had undergone surgical resection was confirmed through the epilepsy surgery program at our hospital.[35]

This study was approved by and adhered to the guidelines established by our hospital's Human Research Protection Center (rms2 No; 2018-31-0925, irb; 2015-0925-004).

MRI and clinical characteristics

Initial MRI examinations were performed using a 1.5-Tesla scanner and follow-up MRI examinations were performed using a 3.0-Tesla scanner in most all patients who were monitored in the out-patient clinic. The diagnostic criteria for HA on the brain MRI included an increased signal on T2-weighed fluid-attenuated inversion recovery images and atrophy of the hippocampus on T1-weighted images with 3-dimensional volume acquisition in oblique coronal images and on T1-weighted axial images. HA was qualitatively confirmed in the brain MRI by one neuroradiologist and one expert epileptologist who were blinded to the patient's medical history. Patients with non-HA lesions, including associated atrophy of the temporal lobe, were excluded. Demographic data, such as sex, age at the onset of epilepsy, and symptom duration, were compared between the CNS infection and conventional groups. Symptom duration was defined as the age of epilepsy onset to the age of registration. Antecedent etiologies of epilepsy, including perinatal insult, complex FS, family history of epilepsy, and head trauma with loss of consciousness, were compared between the two groups. Semiological characteristics of TLE, such as aura and automatism, were also analyzed. If the primary feature of the aura was limbic in nature, even in combination with nonspecific aura, then it was regarded as limbic aura. Automatism was divided into four categories: oropharyngeal, gestural, verbal, and wandering types. The proportion of each type and presence of multiple types of automatism in each patient were analyzed among the patients showing automatism. General characteristics of seizures, such as accompanying secondary generalized tonic-clonic (GTC) seizures, clustering nature, and nocturnal predominance, were analyzed. The definition of clustering[36] was a closely grouped series of seizures or an increase over the patient's typical seizure frequency. Nocturnal predominance was defined as more than 90% of habitual seizures occurring during sleep. Left, right, and bilateral HA on MRI were also compared to assess laterality.

Prognostic criteria for the medical and surgical treatments

Medical and surgical prognoses were separately analyzed. The medical prognosis was categorized as seizure-free and yearly, monthly, weekly, and daily attacks based on the mean frequency of seizure events in patients during the study period, which was counted for 3 years at the end point of study in patients with reliable compliance with antiepileptic drug (AED) treatment. Monthly attacks were defined as more than 4 seizures per month. Twelve to 50 seizure attacks per year and less than 12 seizure attacks per year were regarded as 'weekly attacks' and 'monthly attacks,' respectively. In the patients with a clustering nature, the total number of seizure attacks during clustering events was considered. Patients who were 'seizure-free' or experienced 'yearly attacks' had good outcomes, whereas other patients were classified as having poor outcomes. The minimum duration of follow-up after the surgery was based on at least 2 years. Seizure outcomes were assessed according to Engel's classification[37] [class I, seizure-free; class IA, no disabling seizures; class II, rare seizures (fewer than three seizures per year); class III, worthwhile improvement (reduction in seizure frequency of 80% or more), class IV, no benefit]. Engel's classes I and II were considered good outcomes, and Engel's classes III and IV were considered poor outcomes. The mean number of AEDs administered as part of medical treatment was compared between the two groups at the decision point based on the aforementioned prognostic criteria.

Statistical analysis

Unpaired T-tests were used to compare the demographic characteristics of the subjects, and the chi-square test was used to compare the clinical characteristics of seizures, HA laterality on the brain MRI, and surgical and medical prognoses between the two groups. A univariate logistic regression analysis was performed to reveal the prognostic covariates. For the prognostic covariates, multiple logistic regression tests were conducted to identify the prognostic factors in all patients to correct for the effect of the group. Statistical analyses stratified according to the prognostic criteria of medical and surgical treatments were compared between two groups. SAS software (version 26.0, SAS Institute, Cary, NC, USA) was used for the statistical analyses.

RESULTS

The overall mean age at epilepsy onset was 19.1±14.8 years and 17.8±11.5 years in the CNS infection group and the conventional group, respectively (Table 1). However, among the patients receiving medical treatment alone (Table 2), the mean age at epilepsy onset of patients with unilateral HA in the CNS infection group was 16.3±13.7 years (29.4±26.3 years for bilateral HA) and 19.9±16.9 years for patients in the conventional group. The overall symptom duration was 10.1±9.4 years and 12.2±11.2 years in the CNS infection and the conventional group, respectively. Significant differences in these demographic data were not observed between the two groups (Table 1). The overall mean age at infection was 13.7±11.6 years in the CNS infection group and the latent period was 5.5±5.8 years. When considering patients who only received medical treatment (Table 2), the mean age of the CNS infection group with unilateral HA was 10.4±9.8 years

Table 1. Comparison of the demographic data and clinical characteristics between patients with CNS infection-related and conventional MTLE with isolated HA

Clinical variables	CNS infection-related MTLE with HA group (*n*=54)	Conventional MTLE with HA group (*n*=155)	*p**/*p*†
Demographic data			
Sex (male:female), *n*	34:20	75:80	NS/NS
Mean age at CNS infection±SD (range), year	13.7±11.6 (0.1–61)		
Mean age at epilepsy onset±SD (range), year	19.1±14.8 (1–62)	17.8±11.5 (1–69)	NS/NS
Mean latent period from CNS infection to seizure onset, year	5.5±5.8 (3–15)		
Mean duration of symptoms±SD (range), year	10.1±9.4 (5–12)	12.2±11.2 (4–16)	NS/NS
Presence of seizures at the time of CNS infection, *n* (%)	35/46‡ (76.1)		
Mean follow-up duration±SD (range), month	92.6±68.3 (36–198)	83.6±66.4 (37–201)	NS/NS
Antecedents of epilepsy, *n* (%)			
Febrile seizure	8 (14.8)	68 (43.9)	<0.001/NS
Perinatal insult	1 (1.9)	1 (0.6)	NS/NS
Family history	3 (5.5)	5 (3.2)	NS/NS
Head trauma	4 (7.4)	18 (11.6)	NS/NS
Clinical characteristics of seizures, *n* (%)			
Aura	40 (74.1)	119 (76.8)	NS/NS
Limbic aura	25 (62.5)	81 (68.1)	NS
Automatism	43 (79.6)	115 (74.2)	NS/NS
Type§: oropharyngeal	39 (52.7)	88 (42.7)	NS
Gestural	23 (31.1)	74 (35.9)	
Verbal	9 (12.2)	27 (13.2)	
Wandering	3 (4.1)	17 (8.3)	
Multiplicity: one type	19 (44.2)	41 (35.7)	NS
Two types	18 (41.8)	59 (51.3)	
Three types	5 (11.6)	13 (11.3)	
Four types	1 (2.3)	2 (1.7)	
Secondary generalized tonic-clonic seizure	35 (57.1)	119 (80.3)	NS/NS
Clustering nature	8 (12.2)	19 (15.4)	NS/NS
Nocturnal dominancy	3 (10.2)	14 (11.1)	NS/NS
Laterality of HA on the brain MRI, *n* (%)			
Right	22 (40.7)	78 (50.3)	<0.001/NS
Left	18 (33.3)	77 (49.7)	
Bilateral	14 (25.9)	0 (0.0)	

*Demographic data were compared using an unpaired *t*-test and the chi-square test was performed to compare the clinical characteristics of seizures, †A binary logistic regression analysis with all the prognostic factors was performed, ‡The history of seizures at the time of CNS infection was not clear in eight of the 54 patients, §The proportion was calculated from the sum of each type in patients presenting automatism.
CNS: central nervous system, HA: hippocampal atrophy, MTLE: medial temporal lobe epilepsy, NS: not significant.

with a latent period of 6.2±7.8 years, but the mean age of the CNS infection with bilateral HA was 27.4±25.2 years with a latent period of 2.0±3.7 years. Among patients who underwent surgery (Table 3), the mean age at epilepsy onset was 14.5±13.8 years and 14.6±12.8 years in the CNS infection group and the conventional group, respectively. The mean age at CNS infection and the latent period were 6.9±5.7 and 7.5±6.9 years, respectively (Table 3). A history of seizure at the time of CNS infection was reported in 35 of 46 patients (76.1%) in the CNS infection group. The antecedent etiology, except for FS, did not significantly differ. Sixty-eight of the 155 patients (43.9%) in the conventional group experienced complex febrile convulsions. Demographic data, including sex and age at epilepsy onset, did not show significant differences. In terms of the clinical characteristics of the seizures, significant differences in the proportion of aura, including limbic nature and automatism, were not observed between the two groups. The proportion and presence of multiplicity in each patient presenting automatism were not significantly different between the two groups. Oropharyngeal automatism and a multiplic-

ity of two different types of automatism were most common when the patterns from both groups were combined (Table 1). The general characteristics of the seizures, such as secondary GTC, clustering nature, and nocturnal predominance, also did not differ between groups (Table 1). In terms of laterality on brain MRI, right HA was observed in 40.7% (22/54)

Table 2. Medical prognosis based on the frequency of seizures for three years at the end point of study in patients with reliable compliance

Demographic data	CNS infection-related MTLE with HA group (*n*=37)		Conventional MTLE with HA group (*n*=93)		*p**
Involvement of HA	unil.	bil.			
Sex (male:female), *n*	16:7	7:7	53:40		
Laterality of HA on the brain MRI (left:right), *n*	8:15	14			
Mean age at CNS infection±SD, year	10.4±9.8	27.4±25.2			0.000
Mean age at epilepsy onset±SD, year	16.3±13.7	29.4±26.3	19.9±16.9		0.000
Mean latent period from CNS infection to seizure onset, year	6.2±7.8	2.0±3.7			0.000
Mean duration of symptoms±SD, year	10.1±9.4	9.3±8.2	11.9±10.8		NS
	Prognosis of unil./bil.	No. of AEDs unil./bil.	Prognosis	No. of AEDs	*p*†
Prognostic criteria: Involvement of HA					
Good prognosis, *n* (%)					NS
Seizure-free	7 (30.4)/2 (14.3)	2.0/3.4	32 (34.4)	1.6	
Yearly	8 (34.8)/7 (50.0)	2.7/2.4	37 (39.8)	2.6	
Poor prognosis, *n* (%)					
Monthly	7 (30.4)/2 (14.3)	3.4/4.5	17 (18.3)	2.8	
Weekly	1 (4.3)/3 (21.4)	4.0/4.5	7 (7.5)	3.3	
Total	23 (100.0)/14 (100.0)	2.8/3.2	93 (100.0)	2.4	

*Demographic data were analyzed using an unpaired *t*-test between patients in the CNS infection group stratified according to unilateral and bilateral involvement, †The chi-square test was used to compare the prognoses between the CNS infection and conventional groups.
AEDs: antiepileptic drugs, bil.: bilateral, CNS: central nervous system, HA: hippocampal atrophy, MTLE: medial temporal lobe epilepsy, NS: not significant, unil.: unilateral.

Table 3. Surgical prognosis at two years of follow-up after epilepsy surgery

Demographic data	CNS infection-related MTLE with HA group (*n*=17)	Conventional MTLE with HA group (*n*=62)	*p**
Sex (male:female), *n*	11:6	22:40	
Laterality of HA on brain MRI (left:right), *n*	10:7	28:34	
Mean age at CNS infection±SD, year	6.9±5.7		
Mean age at epilepsy onset±SD, year	14.5±13.8	14.6±12.8	NS
Mean latent period from CNS infection to seizure onset, year	7.5±6.9		
Mean duration of symptoms±SD, year	9.7±8.8	12.5±11.6	NS
F/U period after surgery±SD, month	57.4±43.1	53.4±42.9	NS
Prognostic criteria‡	**(*n*=16§)**	**(*n*=59§)**	***p*†**
Good outcome, *n* (%)			
Free I	10 (62.5)	35 (59.3)	
Class IA	0 (0.0)	6 (10.2)	
Class II	2 (12.5)	10 (16.9)	NS
Poor outcome, *n* (%)			
Class III	3 (18.7)	7 (11.8)	
Class IV	1 (6.3)	1 (1.7)	
Total	16 (100.0)	59 (100.0)	

*Demographic data were compared using an unpaired *t*-test and the chi-square test was conducted to compare the clinical characteristics of seizures, †The chi-square test was conducted to compare the overall prognosis between patients with CNS infection-related epilepsy and patients with conventional MTLE with HA, ‡Engel's classification[30], §The outcome of surgery was not recorded for one of 17 patients in the CNS infection group and 3 of 62 patients in the conventional group.
CNS: central nervous system, HA: hippocampal atrophy, MTLE: medial temporal lobe epilepsy, NS: not significant.

and 50.3% (78/155) of patients in the CNS infection and conventional groups, respectively. Bilateral HA was observed in 25.9% of patients (14/54) in the CNS infection group. Excluding bilateral HA in the CNS infection group, a significant difference was not observed between the two groups (Table 1). When the responses to medical treatment were divided according to good and poor prognoses, the proportions of patients achieving a good prognosis were 65.2% and 65.3%, and the proportions of patients achieving a poor prognosis were 34.7% and 35.7% in the groups with unilateral and bilateral HA, respectively. In the conventional group, the proportions of patients with good and poor prognoses were 74.2% and 25.8%, respectively. No difference was observed between the two groups among patients who received medical treatment. The mean number of AEDs was 3.0 and 2.4 in patients in the CNS infection group and the conventional group, respectively (Table 2). In terms of the surgical prognosis, which was divided into good and poor outcomes, the proportions of patients achieving a good outcome were 75.0% and 86.4% in the CNS infection and the conventional groups, respectively. The proportions of patients in these two groups achieving a poor outcome were 25.0% and 13.5%, respectively. The comparison of surgical prognoses between the two groups did not reveal any significant difference (Table 3). A univariate logistic regression analysis of all the clinical factors between the two groups did not reveal significant prognostic covariates and, naturally, multiple logistic regression analyses did not identify any significant prognostic factors between the two groups.

DISCUSSION

Experimental models[11,20,38] and clinical studies[39,40] suggest the likelihood of a common final pathway for the generation and propagation of seizures, although the clinical profiles of CNS infection might differ, depending on the underlying microorganism. No differences have been revealed between the pathological findings of temporal lobectomy due to intractable seizures after CNS infection and the pathological findings of typical HA,[41] consistent with the results of other reports.[42,43] Although the mechanisms of epileptogenesis with different underlying etiologies have not been clearly elucidated, patients with HA as a relevant lesion resulting from CNS infection-related epilepsy or as a main pathology of conventional MTLE showed similar clinical profiles in this study, which confirmed the probability of a common final pathway of epileptogenesis.

In terms of the antecedent etiology related to epilepsy, no differences, except for FS, were observed between the CNS infection group and the conventional group in the present study. Controlled studies[24] have shown that perinatal risk factors are not risk factors for complex partial seizures, consistent with the results of the present study. In terms of febrile illness, the nature of FS and seizure at the time of CNS infection in CNS infection group were easily differentiated in a timely manner. Because the ability to ascertain the complex nature of FS was limited in some patients due to the very old medical history, only the patients with clearly documented cases of the complex nature of FS were included in the conventional group. Therefore, the proportion was lower than in other reports.[5,8] Nonetheless, the proportion of patients with seizures at the time of CNS infection and the proportion of patients with FS in the conventional group were significantly higher than patients with the other antecedent etiologies in this study. Therefore, acute seizures caused by febrile insults in the brain may represent a plausible etiological mechanism of epileptogenesis in the medial temporal structure, particularly in the hippocampus.

In terms of the clinical characteristics of TLE, the prevalence of aura in the two groups was consistent with other reports.[3] The proportion of patients with limbic aura was also not significantly different between the two groups, and an epigastric rising sensation was the most commonly observed in both groups (data not shown), consistent with other reports of MTLE.[23,44-46] The pattern and proportion of automatism were similar between the two groups, which was also consistent with other studies.[46,47] A statistical analysis including all the clinical factors, including CNS infection as a plausible negative prognostic factor, suggested the presence of similar demographic and clinical characteristics between the two groups. An analysis of the prognosis between the two groups based on good or poor prognosis among patients who received medical treatment and good or poor outcomes among patients who received surgical treatment did not reveal significant differences, and the proportions of seizure-free patients who received medical treatment in the two groups were not substantially different from the values reported in a study with 27.3 years of follow-up.[48] Based on the shorter duration for the development of epilepsy with a mean of only 2 years and the lower proportion of seizure-free patients in the CNS infection group with bilateral HA than among patients with unilateral HA, bilateral HA appeared to indicate a poor prognosis. Nevertheless, the overall prognosis of patients receiving medical treatment was not significantly different, indicating that bilateral HA was not a poor prognostic factor in this study. A greater number of AEDs was needed to achieve a similar medical prognosis in patients with bilateral HA than in the patients with unilateral HA in the CNS group. Symptom duration, which has been reported as a strong negative prognostic factor,[49,50] was not considered a prognostic covariate due to the lack of a significant difference between the two groups. Inter-

estingly, the age at epilepsy onset in patients in the CNS infection group with bilateral HA was significantly older than patients with unilateral HA, but the prognostic significance was not clear. However, an inevitable limitation was associated with the visual analysis of MRI, particularly the bilateral HA, and a 3-dimensional volumetric analysis of the asymmetry of HA might provide more detailed information about the bilateral involvement of HA, which would provide more reliable results.

In conclusion, significant differences in the clinical characteristics or overall prognosis were not observed between patients with HA arising from a CNS infection or conventional MTLE-HA. CNS infection alone and bilateral HA within the CNS infection group were not negative prognostic factors between the two groups. Based on these results, HA might be attributed to the relevant lesion of MTLE with a common epileptogenic pathway due to an underlying febrile insult, which was a common event in both the CNS infection and conventional groups.

In terms of classifying MTLE based on symptomatic localization-related epilepsy, CNS infection-related MTLE-HA might be regarded as another subtype of MTLE with HA with a different underlying etiology.[14] Further studies of patients with different etiologies, including patients with nonlesional MTLE, may provide more conclusive results.

Author Contributions

Conceptualization: Soochul Park. Data curation: Won-Joo Kim, Seung-Koo Lee, Soochul Park. Methodology: Soochul Park. Writing—original draft: Soochul Park. Writing—review & editing: Won-Joo Kim, Seung-Koo Lee, Jin Woo Chang.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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