Microbleeds in the Corpus Callosum in Anoxic Brain Injury
저산소 뇌 손상에서의 뇌량 미세출혈

Chang Su Kim, MD1, Dong Woo Park, MD1*, Tae Yoon Kim, MD1, Young-Jun Lee, MD2, Ji Young Lee, MD2

1Department of Radiology, College of Medicine, Hanyang University Guri Hospital, Guri, Korea
2Department of Radiology, College of Medicine, Hanyang University Hospital, Seoul, Korea

Purpose This study was performed to evaluate the relationship between callosal microbleeds and anoxic brain injury.

Materials and Methods Twenty-seven patients with anoxic brain injuries were analyzed and retrospectively compared to the control group of patients without a history of anoxic brain injury using Fisher’s exact test regarding comorbidities and cerebral microbleeds. The patient group was subdivided according to the presence of callosal microbleeds. Fisher’s exact test was used to compare the presence of typical MRI findings of anoxic brain injury, use of cardiopulmonary resuscitation, and prognosis. The Mann-Whitney U test was used to compare the interval between the occurrence of anoxic brain injury to MRI acquisition.

Results The prevalence of cerebral microbleeds in the patient group was 29.6%, which was significantly higher than that in the control group at 3.7% (p = 0.012). All cerebral microbleeds in the patient group were in the corpus callosum. Compared with the callosal microbleed-absent group, the callosal microbleed-present group showed a tendency of good prognosis (6/8 vs. 11/19), fewer typical MRI findings of anoxic brain injury (2/8 vs. 10/19), and more cardiopulmonary resuscitation (6/8 vs. 12/19), although these differences did not reach statistical significance (p = 0.35, p = 0.19, and p = 0.45, respectively).

Conclusion Callosal microbleeds may be an adjunctive MRI marker for anoxic brain injury.

Index terms Anoxic Brain Damage; Brain Hemorrhage; Corpus Callosum

INTRODUCTION

Cerebral microbleeds (CMBs) have been increasingly identified with the use of newer MRI methodologies, such as susceptibility weighted image (SWI). CMBs are histopathologically described as clusters of hemosiderin-laden macrophages, which are chronic hemorrhagic residue in brain tissue. It has been reported that CMBs occur in cerebrovas-
cular disease, Alzheimer’s disease, and normal aging (1). Also, it has been recently reported that newly developed CMBs are noted after stroke and cardiac valve surgery (2). One report stated that about 12.9% of CMBs contained intact erythrocytes instead of hemosiderin, which is indicative of acute hemorrhage (3).

Callosal microbleeds (MBs) have been reported occasionally in patients with high altitude cerebral edema (HACE), sepsis, chronic obstructive pulmonary disease (COPD), morphine poisoning, and traumatic brain injury, but the pathogenesis of callosal MBs in these conditions, except traumatic brain injury, is still unclear (4-7). In patients with HACE, which is postulated to be a type of hypobaric hypoxia, MRI studies and autopsies have shown that CMBs and white matter edema occur most often in the corpus callosum (4).

Physiologically, anoxic brain injury (ABI) occurs when mean arterial pressure falls below the lower limit of cerebral autoregulation. To our knowledge, callosal MBs in patients with ABI have not been reported.

The purpose of this study was to present callosal MBs in patients with ABI, and to evaluate the relationship between callosal MBs and ABI.

MATERIAL AND METHODS

STUDY DESIGN AND PATIENT SELECTION

Our Institutional Review Board approved this study, and informed consent was waived because of the retrospective nature of the study design (GURI 2019-08-027-001). From December 2011 to November 2018, 52 patients who suffered ABI after cardiac or respiratory arrest underwent brain MRI for ABI assessment. Among them, 25 patients were excluded from the study because neither diffusion weighted image (DWI) nor SWI were obtained, which could show findings of hyperacute to acute ABI and CMBs, respectively. The MRI data and electronic medical records of the remaining patients were then analyzed.

Twenty-seven patients who were clinically diagnosed with ABI, and who underwent brain MRI, including DWI or SWI, were enrolled in our study. None of them had any previous history of HACE, sepsis, COPD, morphine poisoning, or traumatic brain injury. The patient group consisted of 20 men and seven women, with ages ranging from three days to 83 years [median age (interquartile range), 49 (33–67 years)]. To identify the normal control group, we performed a computerized search of the radiology database at our hospital for one month in May 2017 to find patients who underwent brain MRI. Among them, 167 patients who underwent brain MRI, including SWI and DWI, were reviewed. Among them, 27 age- and sex-matched patients without any history of HACE, sepsis, COPD, morphine poisoning, or traumatic brain injury were enrolled randomly for comparison. The control group consisted of 20 men and seven women, ranging from nine days to 83 years [median age (interquartile range), 47 (30–65 years)].

In line with a previous study, prognosis was classified as “good outcome” or “poor (unfavorable) outcome” according to modified Rankin scale score at discharge (8).

MRI PROTOCOL

All scans were performed on a 3 Tesla-MR imaging scanner (Achieva; Philips Medical Systems, Best, the Netherlands), using a receive-only, 32-channel, phased-array coil. Images were
obtained using the following protocols: pre-enhanced T1 weighted image (T1WI); pre-enhanced T2WI; pre-enhanced T2 fluid-attenuated inversion recovery (FLAIR) images; SWI; and DWI. Parameters for the sequences in this study were as follows: SWI: echo time (TE), 0 ms; repetition time (TR), 33 ms; flip angle, 17°; section thickness, 3.0 mm; T1WI: TE, 5 ms; TR, 8 ms; flip angle, 8°; section thickness, 2.0 mm; T2WI: TE, 97 ms; TR, 3000 ms; flip angle, 90°; section thickness, 5.0 mm; T2 FLAIR: TE, 134 ms; TR, 11000 ms; flip angle, 90°; section thickness, 5.0 mm; DWI: TE, 89 ms; TR, 6984 ms; flip angle, 90°; section thickness, 3.0 mm.

IMAGE INTERPRETATION

According to recommended criteria by Greenberg et al. (1), signals from CMBs should be black or profoundly hypointense on T2-weighted MRI; round or oval, blooming, and devoid of hyperintensity on T1WI or T2WI; and at least half of the boundary should be surrounded by brain parenchyma. Various size cut-off points have been suggested for discriminating MBs from macrobleeds, generally ranging up to a maximum diameter of 5 to 10 mm, and, in some studies, a minimum diameter of 2 mm (1). Thus, we defined small round hypointense lesions on SWI in the corpus callosum as callosal MBs. In addition, we determined the distribution of callosal MBs according to the three subdivisions as the rostrum and genu, the body and the splenium on the axial plane of SWI.

Small vessel disease is often sensitively diagnosed by MRI. These MRI markers include white matter hyperintensities of presumed vascular origin, recent small subcortical infarcts and lacunes, CMBs, perivascular space, cortical superficial siderosis, brain atrophy, and cerebral microinfarcts (9). Because short penetrating arterioles of < 100 μm in diameter, supplying corpus callosum, have abundant anastomosis and are not prone to atherosclerotic change, CMBs as image marker of small vessel disease are rarely seen in corpus callosum (10).

As a result of ABI, extensive cytotoxic edema from global hypoxic-ischemic injury shows restricted diffusion in the cerebral cortex, basal ganglia, or cerebellar hemispheres, with consequitively increased T2 signal changes and swelling, which is regarded as a typical imaging finding of ABI in hyperacute to subacute stage (11).

Two radiologists, who were blinded to patient information, evaluated the MR images for the presence of callosal MBs and typical findings of ABI. Any differences between the two radiologists’ findings were then resolved by consensus.

STATISTICAL METHODS

Fisher’s exact test was used to compare age, sex, comorbidities, and the presence of CMBs between the patient and control groups. Fisher’s exact test was also used to compare the presence of typical ABI MRI findings, the use of cardiopulmonary resuscitation (CPR), and prognosis (“good” or “poor”) between the callosal MB present and callosal MB absent groups. The Mann-Whitney U test was used to compare the interval between the occurrence of ABI to MRI between the callosal MB present and callosal MB absent groups. Statistical significance was assigned to differences with a p-value of 0.05 or less. Odd ratios (ORs) were reported with their associated 95% confidence intervals (CIs).
RESULTS

Among the patient group, four patients had small vessel disease and hypertension, one patient had small vessel disease and diabetes mellitus, one patient had only diabetes mellitus, nine patients showed only small vessel disease, and the rest had none of the assessed comorbidities. Among the control group, three patients had small vessel disease and hypertension, one patient had small vessel disease and diabetes mellitus, one patient had only diabetes mellitus, nine patients showed only small vessel disease, and the rest had none of the assessed comorbidities. Between the patient group and control group, there was no statistically significant difference in age, sex, or also risk factors for CMBs, including small vessel disease, hypertension, and diabetes mellitus (Table 1) (12).

Fifteen subjects in the patient group suffered from cardiac arrest, three suffered from respiratory arrest followed by circulatory arrest, and the rest suffered from pure respiratory arrest. In the patient group, 18 patients with cardiac arrest underwent CPR regardless of whether the cardiac arrest was the primary or subsequent insult. In the other patients with pure respiratory arrest, CPR was not carried out. None of the patients in the control group suffered from any type of arrest or underwent CPR. Eight patients (29.63%) of the patient group were classified as the callosal MB present group (Figs. 1, 2). There was cardiac arrest in six of eight patients in the callosal MB present group. Pure respiratory arrest occurred in the other two patients. Among the eight patients in the callosal MB present group, two patients had poor outcome according to modified Rankin scale score. One expired, and the other entered a vegetative status. The interval between the onset of the ABI and the acquisition of MR images in the eight patients in the callosal MBs present group ranged from one day to 21 days (mean interval: 10.375 days). The callosal MBs were located especially in the splenium and posterior body. The other 19 patients in the patient group did not have callosal MBs, who were therefore clas-

<p>| Table 1. Comparison of Demographic Characteristics and Cerebral Microbleeds between the Control and Patient Groups |
|-------------------------------------------------|-------------------------------------------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Patient Group</th>
<th>Control Group</th>
<th>p-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>27</td>
<td>27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR), years</td>
<td>49 (33–67)</td>
<td>47 (30–65)</td>
<td>0.530</td>
</tr>
<tr>
<td>Ranges, days–years</td>
<td>3–83</td>
<td>9–83</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>20 (74.1)</td>
<td>20 (74.1)</td>
<td>1.000</td>
</tr>
<tr>
<td>Women</td>
<td>7 (25.9)</td>
<td>7 (25.9)</td>
<td></td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small vessel disease</td>
<td>14 (51.9)</td>
<td>13 (48.1)</td>
<td>0.500</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4 (14.8)</td>
<td>3 (11.1)</td>
<td>0.500</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2 (7.4)</td>
<td>2 (7.4)</td>
<td>0.695</td>
</tr>
<tr>
<td>Cerebral microbleeds</td>
<td>8 (29.6)</td>
<td>1 (3.7)</td>
<td>0.012</td>
</tr>
</tbody>
</table>

Data are n (%) unless otherwise specified.
*p-values were derived from the Fisher’s exact test.
IQR = interquartile range
sified as the callosal MB absent group. In the callosal MB absent group, CPR was performed in 12 patients, which included nine patients with cardiac arrest and three patients with respiratory arrest followed by circulatory arrest. Eight patients in the callosal MB absent group had poor outcomes according to modified Rankin scale score; one expired, and the other seven patients entered a vegetative state. In those eight patients from the callosal MB absent group with poor outcome, seven patients showed typical MR findings of ABI. Additionally, three patients in the callosal MB absent group with good outcomes showed typical MR findings of ABI. The interval between the onset of the ABI and the acquisition of MR images in the callosal MB absent group ranged from one day to 35 days (mean interval: 12.421 days) (Table 2). In the control group, only one patient (3.7%) showed CMBs in the left centrum semiovale on SWI.

The patient group demonstrated a higher frequency of CMBs than the control group (OR, 10.95; 95% CI: 1.26, 95.06; p = 0.012). The patients in the callosal MB present group demonstrated good outcomes compared with the callosal MB absent group; however, these differences were not statistically significant (OR, 0.46; 95% CI: 0.07, 2.89; p = 0.349). Two patients from the callosal MB present group and 10 patients from the callosal MB absent group showed typical MRI findings of ABI. However, these differences did not reach statistical significance (OR, 0.30; 95% CI: 0.05, 1.88; p = 0.189). Patients in the callosal MB present group underwent CPR with a higher frequency, although this difference was not statistically significant (OR, 1.75; 95% CI: 0.28, 11.15; p = 0.450). There was no significant difference in the interval from the ABI to MRI acquisition between the callosal MB present and callosal MB absent groups (p = 0.402).

**DISCUSSION**

In HACE and morphine poisoning, the mechanism of CMBs is based on disruption of the...
Fig. 1. A 61-year-old man with anoxic brain injury due to cardiac arrest. This patient underwent cardiopulmonary resuscitation and successfully recovered without significant neurologic sequelae. The interval from the event of ABI to MRI acquisition was 17 days.
A. The SWI magnitude image shows several tiny, round hypointense lesions in the corpus callosum splenium, which are callosal microbleeds.
B. The T2 FLAIR images show cerebral atrophy and white matter hyperintensities as manifestations of small vessel disease.
ABI = anoxic brain injury, FLAIR = fluid-attenuated inversion recovery, SWI = susceptibility weighted image

Fig. 2. A 33-year-old man with anoxic brain injury due to cardiac arrest. This patient underwent cardiopulmonary resuscitation and was successfully recovered without significant neurologic sequelae. The interval from the event of ABI to MRI acquisition was 14 days.
A. The SWI magnitude image shows several tiny, round hypointense lesions in the corpus callosum posterior body and splenium, which are callosal microbleeds.
B. No obvious abnormalities were noted on the T2 FLAIR images.
ABI = anoxic brain injury, FLAIR = fluid-attenuated inversion recovery, SWI = susceptibility weighted image
blood-brain barrier. Particularly in HACE, venous hypertension leads to transmigration of erythrocytes and blood degradation products into the perivascular space. Venous hypertension can be induced by venous outflow obstruction due to anatomical variation, high altitude pulmonary edema, or cerebral venous thrombosis, which is related to volume depletion and polycythemia (4). In morphine poisoning, reduced breathing leads to an increase in PaCO₂, and consecutive increases in cerebrospinal fluid and intracranial pressure (7). These additional mechanisms are considered to be hallmarks of CMBs. However, the reason for the predilection of callosal MBs in HACE remains controversial. The corpus callosum might be susceptible to hypoxic vasodilatation, autoregulatory failure, and overperfusion, due to small, short, perforating supplying arteries, and lack of adrenergic tone (2-4, 7). Therefore, it can be postulated that the pathogenesis of callosal MBs in ABI is mainly increased permeability due to disruption of the blood-brain barrier and hypoxic vasodilatation. In our study, callosal MBs were noted especially in the splenium and posterior body. We also postulate that hyperperfusion is one of the mechanisms making callosal MBs similar to morphine poisoning. Unlike other pericallosal arteries branching off of the anterior cerebral arteries, posterior pericallosal arteries from the posterior cerebral arteries specifically supply the splenium of the corpus callosum (13). Therefore, the vessel anatomy of the corpus callosum may play a role in the predilection of callosal MBs to occur in the splenium.

Although the prevalence of callosal MBs in the overall population has not been reported, the prevalence of CMBs has been reported at 6.5% in an overall population with an average age 60 years in the Austrian Stroke Prevention study (14), and 3.1% in healthy Japanese adults with an average age of 52.9 years (14-16). The latter percentage roughly corresponds to the prevalence of CMBs in the control group in the present study. In our study, there were also more CMBs in the patient group than the control group (29.63% vs. 3.7%, respectively; p = 0.012). Additionally, considering that the CMBs in the control group were located only in the centrum semiovale, CMBs in the corpus callosum may be a more distinguishing feature of ABI.

Two of eight patients (25%) in the callosal MB present group showed typical MRI findings, compared to 10 out of 19 patients (52.6%) in the callosal MB absent group. There might be a tendency for patients in the callosal MB present group to show typical MRI findings of ABI less frequently and good outcomes more frequently than patients in the callosal MB absent group. Therefore, CMBs in those patients with ABI may represent a mild form of ABI due to the disruption of the blood-brain barrier, rather than cytotoxic edema. Comparison between the callosal MB present and callosal MB absent groups showed patients in the callosal MB present group had a higher frequency of CPR, although that difference wasn’t statistically significant (OR, 1.75; 95% CI: 0.28, 11.15; p = 0.450). Although intracranial pressure is not increased after CPR, there have been several reports that blood-brain barrier disruption is noted after CPR and/or adrenaline usage in piglets (17-20). To our knowledge, the relationship between CPR and CMBs in human has not been reported yet. On the other hand, patients who are in cardiac arrest must undergo CPR, regardless of whether the cardiac arrest is the primary insult or secondary to respiratory arrest. This means that the callosal MB present group had a lower proportion of patients with pure respiratory arrest. Pure hypoxic insult does not commonly lead to severe brain injury, even in prolonged and/or extreme hypoxia. Pure respiratory arrest often leads to transient brain dysfunction, resulting in less severe and permanent brain
Microbleeds of the Corpus Callosum in Anoxic Brain Injury

Injury, than that caused by cardiac arrest (21). This is inconsistent with the tendency that patients in the callosal MB present group showed a better prognosis than patients in the callosal MB absent group. Further study is needed to understand this relationship.

Additionally, there are differences in the distribution of CMBs among patients with ABI and other pathological conditions, such as hypertensive microangiopathy, cerebral amyloid angiopathy, and traumatic brain injury, which show manifestations of CMBs. In hypertensive microangiopathy, CMBs are typically located in the basal ganglia, pons, and cerebellum. In cerebral amyloid angiopathy, CMBs tend to occur at the gray-white matter junction, sparing the basal ganglia and pons. In traumatic brain injury, hemorrhagic diffuse axonal injury may represent CMBs, which are typically located in the corpus callosum and gray-white matter junction with more radial configurations conforming to the perivascular space (22). Thus, according to medical history and the typical distribution of CMBs, the differential diagnosis of these patients’ pathological conditions can be achieved.

There are some limitations to this study. First, the sample size was too small to show statistically significant differences in prognosis, typical MRI findings of ABI, and the occurrence of CPR between the callosal MB present and callosal MB absent groups. More studies with larger populations are needed to evaluate the presence of statistically significant differences. Second, there might be a selection bias, because those patients with ABI who could undergo time-consuming MRI, including SWI, might have had a less severe clinical status than patients who could not. Furthermore, the different proportion of patients who underwent CPR, cardiac or respiratory arrest, could be confounder. Thus, the relationship between callosal MBs and more severe ABI need to be further studied. Third, the electronic medical records of enrolled patients were not perfect. Fourth, the stage of callosal MBs could not be assessed exactly because of the absence of complete, previous SWI. However, the callosal MBs in this study were probably recent MBs, because callosal MBs have not been reported previously as incidental findings and, moreover, these patients had no previous history of HACE, sepsis, COPD, morphine poisoning, or traumatic brain injury (23). Furthermore, callosal MBs are hardly seen in small vessel disease. Fifth, imaging findings were only investigated for presence or absence. If grading for ABI or small vessel disease such as Fazekas scale is applied, it can be more delicate result. However, it couldn’t be possible due to small sample size.

In conclusion, our study suggests that there is a higher prevalence of CMBs in patients with ABI than those without ABI. Moreover, in ABI patients with CMBs, all CMBs were confined to the corpus callosum. This study implies that ABI could show callosal MBs similar to HACE and morphine poisoning. These callosal MBs often exist in patients who are survived from ABI without significant sequelae of extensive encephalopathy. Thus, callosal MBs may be an adjunctive MRI marker for ABI and may be of value in predicting ABI prognosis.

Author Contributions

Conflicts of Interest
The authors have no potential conflicts of interest to disclose.
Acknowledgments

The authors would like to thank research professor Eunwoo Nam for grateful statistical consultation.

REFERENCES

6. Corrêa DG, Cruz Júnior LC, Bahia PR, Gasparetto EL. Intracerebral microbleeds in sepsis: susceptibility-weighted MR imaging findings. Arq Neuropsiquiatr 2012;70:903-904
저산소 뇌 손상에서의 뇌량 미세출혈

김창수1 · 박동우1* · 김태윤1 · 이영준2 · 이지영2

목적 뇌량 미세출혈이 저산소 뇌 손상과 상관관계가 있는지 알아보고자 하였다.
대상과 방법 임상적으로 진단된 27명의 저산소 뇌 손상 환자군을 대상으로 후향적으로 연구를
진행하였다. 나이와 성별을 매칭한 대조군과 Fisher's exact test로 동반 질환, 뇌 미세출혈 유무를 비교하였다. 환자군은 뇌량 미세출혈의 유무로 나누어 비교하였다. Fisher's exact test로 두 그룹 간의 저산소 뇌 손상의 전형적인 자기공명영상 특징 유무, 심폐소생술 유무, 예후 정도를 비교하였고, Mann-Whitney U test로 저산소 뇌 손상 사건 발생 후 자기공명영상 획득까지의 시간 간격을 비교하였다.
결과 환자군에서 뇌 미세출혈은 29.6%에서 보였으며, 이는 대조군의 3.7%보다 통계적으로 유의하게 높았다(p = 0.012). 환자군에서의 모든 뇌 미세출혈은 뇌량에 국한됐다. 비뇌량 미세출혈군과 비교하여, 뇌량 미세출혈군은 좋은 예후를 보이는 경우가 많았고(6/8 vs. 11/19), 저산소 뇌 손상의 전형적인 자기공명영상 특징을 작은 비율에서 보이며(2/8 vs. 10/19), 심폐소생술이 많은 비율에서 시행됐으나(6/8 vs. 12/19) 통계적 유의성을 보이지 못하였다(p = 0.35, p = 0.19, p = 0.45, respectively).
결론 뇌량 미세출혈은 저산소 뇌 손상을 시사하는 부수적인 자기공명영상 특징이 될 수 있겠다.

1한양대학교 의과대학 구리병원 영상의학과, 2한양대학교 의과대학 한양대학교병원 영상의학과