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Decreased Bone Marrow Activity Measured by Using ^{18}F-fluorodeoxyglucose Positron Emission Tomography among Patients with Cerebral Atherosclerosis

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Background: We investigated bone marrow activity among patients with subclinical cerebral atherosclerosis.

Methods: Between January 2011 and December 2014, the patients who had undergone both brain computed tomography angiography (CTA) and whole body ^{18}F-fluorodexoyglucose (FDG) positron emission tomography (PET) from health promotion center in a tertiary university hospital were included. Intracranial cerebral artery atherosclerosis was diagnosed using CTA, and bone marrow activity was measured using FDG PET from the 4th and 5th lumbar vertebral bodies. Cerebral artery vessel wall activity was measured from the cavernous portion of the internal carotid arteries (ICA). The maximal standardized uptake values of the vertebrae and target to background ratio of the vessel walls were compared by the Mann-Whitney *U* test among the patients with and without intracranial atherosclerosis.

Results: We identified 20 patients (mean age, 60.9±13.9 years; including six women) and seven of them were diagnosed with cerebral atherosclerosis. The cavernous ICA showed increased FDG uptake among the patients with cerebral atherosclerosis (1.08±0.24 vs. 0.91±0.18, p=0.02). The patients with cerebral atherosclerosis had significantly lower uptake values of FDG at the 4th (1.51±0.38 vs. 1.96±0.52, p=0.01) and the 5th (1.46±0.21 vs. 1.80±0.57, p=0.02) vertebrae.

Conclusion: Intracranial cerebral artery atherosclerosis is associated with decreased FDG uptake in lumbar vertebrae. Further studies are warranted to evaluate pathophysiological link between intracranial atherosclerosis and bone marrow activity.

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INTRODUCTION

Inflammation of arterial wall is an essential step for the initiation and progression of atherosclerosis and the monocyte derived macrophages from the bone marrow or spleen are known to be the principal mediators of atherosclerosis-related inflammation.[1-3] Animal studies have shown that monocyte recruitment from the spleen is indispensable for chronic atherosclerosis progression and heart failure aggravation after myocardial infarction.[4,5] Recently several human studies disclosed that the activity of the hematopoietic organs measured by ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) is increased after acute myocardial infarction, which suggests active recruitment and migration of the inflammatory cells from bone marrow

and spleen.[1,2] However, studies investigating hematopoietic organ activity among patients with cerebral atherosclerosis have not been conducted yet. Therefore, we investigated bone marrow and splenic activity among apparently normal subjects with intracranial cerebral atherosclerosis to disclose whether there exist pathophysiological link between the two distant systems.

SUBJECTS AND METHODS

1. Patient selection

Between January 1st, 2011 and December 31th, 2014, the subjects who had undergone both brain computed tomography angiography (CTA) and whole body FDG PET/computed tomography (CT) from health promotion center were considered eligible to be studied. We included those patients who did not have active cancer or previous stroke history at the time of PET/CT evaluation. We reviewed their demographic variables, vascular risk factors and laboratory data. This study was reviewed and approved by the Institutional Review Board of Chung-Ang University Hospital, and informed consent requirement was exempted because of the retrospective study design ensuring anonymity.

2. Brain CTA

All the patients underwent multidetector CTA using Brilliance 256-channel CT ver. 2.2 (Philips Medical System, Best, the Netherlands) with the following parameters: 120 kVp, 140 mA, 0.9 mm section thickness, 0.9 mm slice acquisition interval, and intravenous administration of 80 mL iohexol (GE healthcare, Milwaukee, WI, USA) at a rate of 4.0–4.5 mL/s. Cerebral atherosclerosis was diagnosed when any major intracranial arteries including the anterior, middle and posterior cerebral arteries, vertebral and intracranial portions of the internal carotid arteries (ICA), and the basilar artery were observed with any degree of focal stenosis or focal eccentric calcification at arterial wall from CT angiography.

3. Whole body PET

Whole body PET-/CT was performed using combined PET/CT scanner (Gemini TF 16, Philips Medical Systems, Cleveland, OH, USA) according to the following protocol. After a minimum 8 hours of fasting, 259–370 MBq (7–10 mCi) of FDG was injected intravenously. Approximately 60 min after injection, PET images were acquired for 5 min/bed for the head and 1 min/bed from the skull base to the proximal thigh, right after CT scanning (120 kVp, 50 mA). Since the intracranial portion of the ICA before bifurcation passes through the bony carotid canal which isolates vascular structure from the brain parenchyma, and the cavernous portion of the ICA is the most vulnerable site for atherosclerotic calcification,[6,7] we measured vessel wall activity by FDG-PET from cavernous portion of the ICA. Extracranial proximal ICA wall activity was also measured at the bifurcation site. The maximum standard uptake value (SUV) of arterial wall was divided by blood-pool SUV measure at the descending aorta for normalization, which derives the arterial wall target-to-background ratio (TBR). FDG uptake was measured in the spleen and the lumbar vertebrae by placing a region of interest around the organ on all trans-axial slices, and the highest mean SUVs were selected. The two independent investigators (E.S.L. and J.W.S.) who were unaware of atherosclerosis status analyzed PET imaging data.

4. Statistical analyses

Descriptive data were presented as mean±standard deviation for continuous variables or the number of patients for categorical variables. The continuous variables were compared by the Mann-Whitney *U* test, and the Fisher exact test was performed to compare dichotomous variables. Two-tailed values were reported and statistical significance was defined as $p<0.05$. The interobserver correlation coefficient values were investigated for every SUV by two-way random effects model with absolute agreement definition and revealed favorable consistency with intra-class correlation coefficients of 0.91 with 95% lower confidence interval of 0.80. For the TBR of intracranial carotid arterial wall, we also performed Bland-Altman method to assess interobserver variability. Since every patient had two ICAs

and intracranial cerebral atherosclerosis was detected in seven patients, the vessel wall activity was compared between 14 sites from patients with cerebral atherosclerosis and 26 sites from patients without it. Spearman's rank correlation was applied to evaluate the correlation between SUV measured at the 5th lumbar vertebra and laboratory variables. All the statistical analysis were performed by SPSS version 22.0 (IBM, Armonk, NY, USA).

RESULTS

Among 22 eligible subjects, 20 were finally included after exclusion of two subjects with previous stroke history (mean age, 60.9±13.9 years, with six female patients) and seven of them had cerebral atherosclerosis (Table 1). Demographic and clinical variables were not significantly different between the included and excluded subjects. The most commonly affected vessels by atherosclerosis were the cavernous portion of the ICA in five patients, and the posterior cerebral artery in one patient, and the vertebral artery in the rest.

The representative whole body FDG PET scans from four different patients from each group showed that the patients with cerebral atherosclerosis had decreased bone marrow activity compared to those of patients

Table 1. Clinical and laboratory variables of the patients with and without intracranial atherosclerosis

	Intracranial atherosclerosis (-)	Intracranial atherosclerosis (+)	*p*-value
Patient number	13	7	
Age, years	59±15	65±12	0.31
Sex (female)	3	3	0.67
Hypertension	5	2	0.99
Diabetes mellitus	3	2	0.99
Previous cancer history	2	1	0.99
Statin medication	4	2	0.99
Body mass index	24.6±4.6	22.9±3.0	0.43
Hematocrit, %	41.1±5.8	40.0±5.5	0.74
Platelet count, $\times 10^9$/L	229±47	253±85	0.80
White blood cell, $\times 10^9$/L	7.3±2.3	6.0±1.5	0.20
Neutrophil, $\times 10^9$/L	4.8±2.1	3.7±0.9	0.44
Lymphocyte, $\times 10^9$/L	1.9±0.6	1.8±0.7	0.76
Total cholesterol, mg/dL	206.2±47.9	165.9±50.7	0.10
LDL cholesterol, mg/dL	118.2±35.2	86.8±11.8	0.11
Fasting blood glucose, mg/dL	107.6±20.2	104.7±13.4	0.91
Blood urea nitrogen, mg/dL	17.4±5.6	14.1±3.8	0.32
Creatinine, mg/dL	1.33±1.93	0.94±0.25	0.36
Serum calcium, mg/dL	9.15±0.54	9.20±0.37	0.73
hsCRP, mg/L	12.8±25.5	1.4±0.9	0.64
TBR cavernous ICA	0.91±0.18	1.08±0.24	0.02
TBR proximal ICA	0.84±0.21	0.92±0.20	0.45
SUV 4th lumbar vertebra	1.96±0.52	1.51±0.38	0.01
SUV 5th lumbar vertebra	1.80±0.57	1.46±0.21	0.02
SUV spleen	0.88±0.17	0.82±0.17	0.35

Values are presented as mean±standard deviation or number.
LDL; low density lipoprotein, hsCRP; high sensitivity C-reactive protein, TBR; target to background ratio, ICA; internal carotid artery, SUV; standard uptake value.

without atherosclerosis (Fig. 1A). The patients with cerebral atherosclerosis had significantly lower mean SUV from the 4th (1.51±0.38 vs. 1.96±0.52, p=0.01) and the 5th vertebra (1.46±0.21 vs. 1.80±0.57, p=0.02, Fig. 1B) compared to those without. However, the activity of spleen was not different between the two groups (0.82±0.17 vs. 0.88±0.17, p=0.35). Demographic variables, vascular risk factor profiles and common blood cell count results were not different, either. Vertebral FDG uptake at the 5th lumbar vertebra showed positive correlation with hematocrit (p=0.005; Spearman's rho, 0.607) and with lymphocyte count (p=0.025; Spearman's rho, 0.499).

Next we studied the vessel wall uptake of intracranial cerebral arteries. The intracranial cerebral arterial wall uptake measured from the cavernous portion of the ICA (Fig. 2A) showed no fixed or proportional biases and the interobserver limit of agreement was 0.048±0.167 by maximum TBR (Fig. 2B). The vessel wall activity was increased in patients with cerebral atherosclerosis (1.08±0.24 vs. 0.91±0.18, p=0.02) compared to those without atherosclerosis (Fig. 2C). The correlation between FDG uptake levels at cavernous ICA and at 5th lumbar vertebra was not significant (Spearman's rho, -0.214; p=0.35).

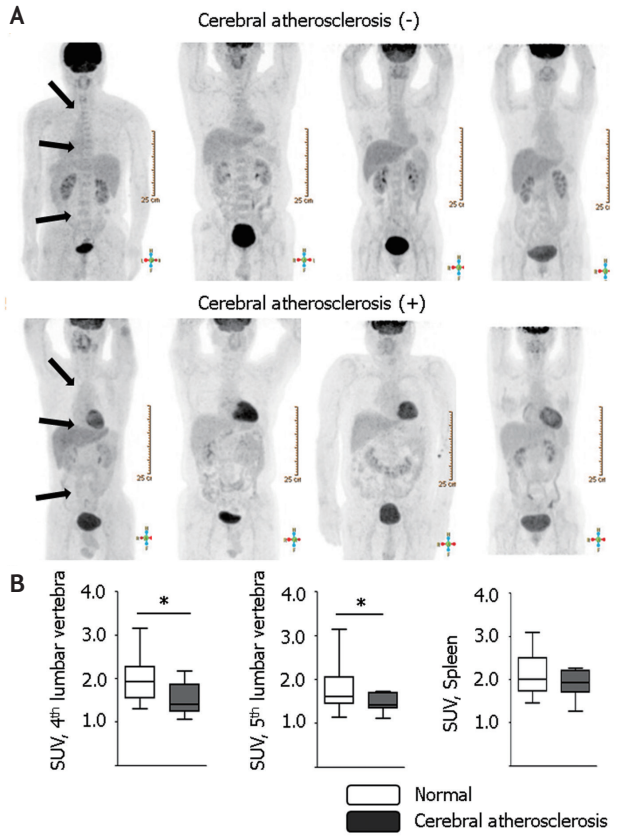

Fig. 1. FDG activity of the bone marrow in terms of intracranial atherosclerosis. Representative whole-body FDG PET/CT scan images of the four patients with and without intracranial cerebral atherosclerosis show that the FDG bone marrow uptake (black arrows) was markedly diminished among patients with cerebral atherosclerosis (A). When the FDG uptake was compared from lumbar vertebrae, the mean standard uptake value of patients with cerebral atherosclerosis was significantly decreased from the 4th (1.51±0.38 vs. 1.96±0.52, p=0.01) and 5th lumbar vertebrae (1.46±0.21 vs. 1.80±0.57, p=0.02) than the value of patients without cerebral atherosclerosis (B). The uptake of the spleen (0.82±0.17 vs. 0.88±0.17, p=0.35) was not different between the two groups (B). SUV; standard uptake value, FDG; ^{18}F-fluorodexoyglucose, PET/CT; positron emission tomography/computed tomography. *Stands for p<0.05.

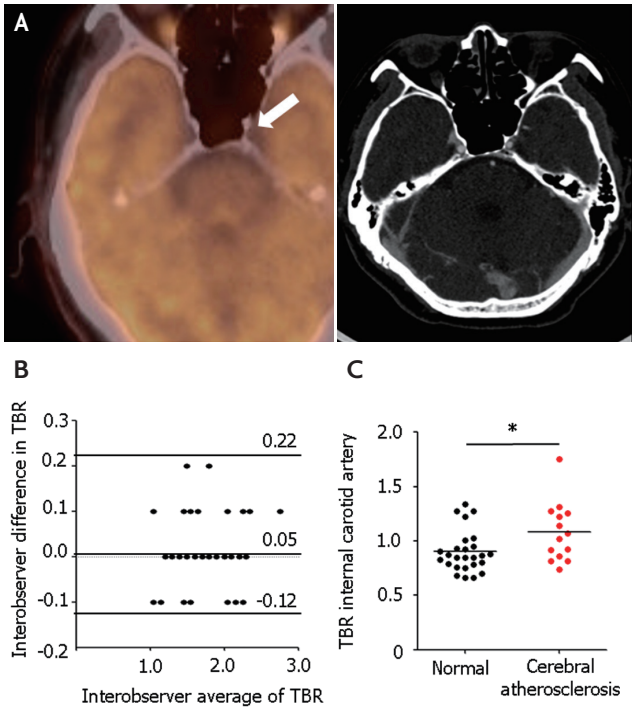

Fig. 2. FDG uptake status of the intracranial cerebral arterial vessel wall and the correlation analysis with bone marrow activity. The cerebral arterial wall activity from FDG PET scan was measured at the cavernous portion of the internal carotid artery (white arrow) (A). Interobserver variability of TBR measurement was assessed by the Bland Altman method, and the difference in each pair of measurements was plotted against the pair's mean (interobserver variability, 0.048±0.088; B). The FDG uptake measured by target-to-background ratio was increased at the cavernous internal carotid arteries from the patients with cerebral atherosclerosis (1.08±0.24 vs. 0.91±0.18, p=0.02; C). TBR; target-to-background ratio, FDG; ^{18}F-fluorodexoyglucose, PET; positron emission tomography.

DISCUSSION

Patients with asymptomatic cerebral atherosclerosis showed decreased bone marrow activity measured from lumbar vertebral bodies, whereas increased uptake of FDG from the cavernous portion of the ICAs was observed. To our knowledge, this is the first study evaluating hematopoietic organ activity among patients with cerebral artery atherosclerosis as well as applying FDG PET technique for assessing intracranial atherosclerosis activity.

Several human studies have evaluated hematopoietic system activity among the patients with coronary artery disease and found increased FDG uptake of the spleen and bone marrow after acute myocardial infarction.[1,2] They also reported positive correlation between FDG uptake at hematopoietic organs and systemic inflammatory markers & carotid arteries.[1,2] One study showed that enhanced hematopoietic organ activity is related to increased future vascular events among patients with coronary artery disease.[2] These studies provided a novel pathophysiologic role of inflammatory cells that originated from hematopoietic organs, which facilitates the development and progression of atherosclerosis.[5] However, our study showed that the patients with asymptomatic cerebral atherosclerosis had decreased bone marrow activity compared to those without, which seems to be contrary to the previous study results obtained from acute myocardial infarction patients. Decreased bone marrow activity could be related to the defective hematopoietic stem cell niche leading to reduced arterial restorative capacity, thereby inducing the progression of cerebral atherosclerosis. An in vivo study suggests protective effect of mobilized hematopoietic stem cells in remodeling of the arterial wall after vascular injury.[8] Another hypothesis is that aging related systemic process initiates atherosclerosis and suppresses bone metabolism. This hypothesis seems plausible as several previous epidemiological data showed paradoxical correlation between vascular calcification representing atherosclerosis burden and bone mineral loss among old population.[9]

The inflammatory activity of atheromatous plaque can represent atheroma vulnerability and the future risk of vascular events.[10] The application of PET with various ligands has been widely accepted in evaluating inflammation activity within atherosclerotic plaque among the patients with coronary artery disease or carotid artery disease.[11,12] We found that the cavernous portion of the ICA could be an appropriate region where FDG uptake could be consistently measured and reflect inflammatory activity of intracranial arterial atherosclerosis. Since our study included only small number of apparently normal subjects with asymptomatic atherosclerosis, future studies are warranted to assess inflammation activity of symptomatic cerebral atherosclerosis by including acute cerebral infarction patients.

Our study has several important limitations. First the number of patients was small, and the patients had heterogeneous medical history that could possibly affect FDG uptake. Although the majority of the patients did not have cancer, three patients had previous cancer history and another patient had rheumatoid arthritis, which might have influenced bone marrow activity. Second, detailed blood inflammatory biomarkers or hematopoietic stem cell markers were not checked because of retrospective study design, which might be helpful to elucidate the mechanism of reduced bone marrow activity among the patients with asymptomatic cerebral atherosclerosis. Lastly, subclinical atherosclerotic burden in other vascular beds, such as coronary artery or peripheral artery had not been examined in the included subjects, which might have affected the study results.

We showed that the patients with intracranial cerebral artery atherosclerosis had decreased bone marrow activity measured by using FDG PET from the lumbar vertebrae and increased vessel wall activity measured from the cavernous portion of the ICA. Further studies are warranted to evaluate the pathophysiological link between intracranial atherosclerosis and hematopoietic organ activity.

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Conflicts of Interest

No potential conflicts of interest relevant to this article was reported.

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