Relations of Serum Soluble E-Selectin and Adiponectin with Enlarged Perivascular Spaces in Patients with Recent Lacunar Infarction

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Enlarged perivascular spaces (EPVS) have recently attracted a lot of attention not only as the cerebral lymphocyte recycle pathway but also as potential new imaging markers of small vessel disease [1–3]. Previous studies in patients with multiple sclerosis once indicated that increased permeability of blood–brain barrier might play a role in the morphological changes in the spaces [4]. However, little evidence was presented for EPVS in patients with ischemic stroke to date.

As we all know, soluble E-selectin (sE-selectin) is specifically expressed by endothelial cells in increased amounts on activation and was considered to be a specific marker of endothelial damage [5,6]. Whereas, adiponectin, synthesized by white adipose tissue [7], exerts an endothelium protective role through multiple intracellular signaling cascades [8,9]. We therefore aimed to evaluate the correlation between serum adiponectin/sE selection concentration and EPVS in patients with recent lacunar infarction to explore the involvement of endothelium to EPVS.

A total of 461 subjects include 321 consecutive patients with first-ever lacunar infarction (based on TOAST classification) within 14 days of onset and 140 age, and sex-matched healthy controls were prospectively derived from Jinling Hospital (Figure S1). The study protocol was approved by the ethical committee of Jinling Hospital, and written informed consent was obtained from each participant.

Blood was sampled from each subject right after admission. SE-selectin and adiponectin were measured with commercially available enzyme-linked immunosorbent assay kits (BMS205INST, Ebioscience, San Diego, CA, USA; EZHMTA-64K, Merck Millipore, Billerica, MA, USA).

Magnetic resonance images were only obtained in patients with recent lacunar infarction by a 3 Tesla system (MAGNETOM Trio 3.0T; Siemens, Erlangen, Germany). EPVS were identified

by their linear, ovoid or round shape, iso-intense to CSF cerebrospinal fluid (T2- hyperintense and T1/FLAIR-hypointense with respect to brain), without signal changes in their rims or adjacent tissue in all pulse sequences with the diameter between 1 mm and 3 mm [10]. EPVS in four imaging slices include centrum semiovale (CS), basal ganglia (BG), hippocampus and mesencephalon were individually evaluated by two experienced neuroradiologists according to the Rotterdam-Graz Dilated Virchow-Robin Spaces Rating Form [10]. The intraclass correlation coefficient (ICC) was calculated in every brain slice, and the final result was reached through consultation.

The comparison of serum sE-selectin/adiponectin between patients and healthy controls were performed by Mann–Whitney *U*-test. Logistic regression model was used to investigate the relationship between the presence of EPVS and serum sE-selectin/adiponectin in each imaging slices, respectively. For the numbers of EPVS, Poisson regression model was employed to calculate the relative risks (RRs) and 95% confidence interval (CI) after adjusting for all the baseline items listed in Table 1. Data were analyzed with SAS 9.1 software (SAS Institute, Inc., Cary, NC, USA).

The median serum sE-selectin (IQR) was 9.1 (11.0) mmol/L in patients and 8.9 (9.7) mmol/L in healthy controls ($P > 0.05$). With respect to adiponectin, the media concentration (IQR) was 597 (707) mmol/L in patients, which is significantly higher than that in healthy controls (804 [726] mmol/L, $P < 0.001$).

The median number (IQR) of EPVS in patients with recent lacunar infarction was 5 (10); 5 (10); 1 (3); 0 (1) in slice of CS, BG, hippocampus and mesencephalon, respectively. The corresponding ICCs were 0.73, 0.71, 0.81, and 0.83 between the two observers. The comparisons of clinical, imaging and blood items between

Table 1 Comparison of baseline items between patients with and without EPVS in the specified slice of brain imaging

	CS (Positive = 240)	BG (Positive = 243)	Hippocampus (Positive = 190)	Mesencephalon (Positive = 124)
Age, year, mean (SD)	62.7 (12.6) ^a	62.5 (12.2) ^a	62.5 (12.6) ^a	63.61 (12.2) ^a
Female, n (%)	66 (27.5)	63 (25.9)	51 (26.8)	34 (27.4)
BMI, kg/m ² , mean (SD)	24.8 (2.5)	25.0 (4.3)	25.0 (2.6)	24.9 (2.5)
NIHSS score, media, (IQR)	3 (4) ^a	3 (3)	3 (4)	2 (4)
Hypertension, n (%)	162 (67.5) ^a	167 (68.7) ^a	120 (63.2)	77 (62.1)
Diabetic, n (%)	51 (21.3)	54 (22.2)	40 (21.1)	32 (25.8)
Hyperlipidemia, n (%)	43 (17.9)	42 (17.3)	33 (17.4)	26 (21.0)
Current smoker, n (%)	97 (40.4) ^a	104 (42.8) ^a	78 (41.1)	59 (47.6) ^a
Brain atrophy, n (%)	75 (31.3) ^a	72 (29.6) ^a	48 (25.3)	33 (26.6)
Days from stroke onset to admission (blood sampling), media, (IQR)	8 (6)	7 (6)	7 (7)	8 (4)
Infarction diameter >15 mm, n (%)	93 (38.8)	91 (37.4)	80 (42.1)	49 (39.5)
Adiponectin, ng/ml, media (IQR)	446 (514) ^a	519 (553) ^a	556 (731)	630 (674)
sE-selectin, ng/ml, media (IQR)	11.2 (10.4) ^a	11.1 (10.8) ^a	9.6 (11.1)	8.4 (10.3)

SD, standard deviation; BMI, body mass index; NIHSS, national institutes of health stroke scale; IQR, interquartile range. ^aIndicates that $P < 0.05$ compared with EPVS negative group in each slice.

patients with and without EPVS in each imaging slice were present in Table 1.

After adjusting for potential confounders, multivariable binary logistic and Poisson regression using the presence and numbers of EPVS as dependent variables indicated that each standard deviation increment of serum SE-selectin positively related to EPVS in CS and BG (OR [odd ratio] 3.83, 95% CI 2.62–5.95; RR 1.71; 95% CI 1.55–1.89 in CS and OR 2.80, 95% CI 2.00–3.90; RR 1.61, 95% CI 1.46–1.77 in BG). Serum adiponectin, on the contrary, was conversely related to EPVS in CS (OR 0.31, 95% CI 0.22–0.43; RR 0.59, 95% CI 0.54–0.65) and in BG (OR 0.53, 95% CI 0.40–0.70; RR 0.73, 95% CI 0.66–0.81). To hippocampus and mesencephalon,

we failed to correlate EPVS to both sE-selectin and adiponectin. (Table 2).

Our preliminary study identified serum sE-selectin and adiponectin were not only associated with the presence of EPVS in CS and BG, but also the numbers of them, suggested a dose-dependent relationship, of which a potential causal association between endothelia dysfunction and EPVS could be inferred, but certainly not established due to the cross-sectional nature of our study.

With respect to EPVS in hippocampus and mesencephalon, the endothelia makers as well as most of the cardiovascular risk factors and imaging items did not correlate with them. Whether our

Table 2 Multivariable analysis of the relationship between per SD increment of sE-selectin/adiponectin and the presence or the number of EPVS in different imaging slices

	Model 1 ^a				Model 2 ^b			
	Logistic regression		Poisson Regression		Logistic regression		Poisson Regression	
	OR	95% CI	RR	95% CI	OR	95% CI	RR	95% CI
Centrum semiovale								
sE-selectin	4.03*	2.81–5.79*	1.77*	1.62–1.95*	3.83*	2.62–5.95*	1.71*	1.55–1.89*
Adiponectin	0.30*	0.22–0.42*	0.58*	0.53–0.64*	0.31*	0.22–0.43*	0.59*	0.54–0.65*
Basal ganglia								
sE-selectin	2.92*	2.13–3.99*	1.70*	1.55–1.87*	2.80*	2.00–3.90*	1.61*	1.46–1.77*
Adiponectin	0.51*	0.39–0.67*	0.71*	0.64–0.78*	0.53*	0.40–0.70*	0.73*	0.66–0.81*
Hippocampus								
sE-selectin	1.00	0.82–1.23	0.97	0.86–1.10	0.98	0.80–1.23	0.94	0.82–1.07
Adiponectin	1.01	0.82–1.24	1.06	0.93–1.19	1.06	0.86–1.32	1.09	0.96–1.25
Mesencephalon								
sE-selectin	1.02	0.83–1.25	1.04	0.90–1.21	1.01	0.81–1.26	0.97	0.84–1.14
Adiponectin	1.07	0.87–1.32	0.99	0.85–1.15	1.14	0.91–1.42	1.05	0.90–1.23

OR, odd ratio; CI, confidence interval; RR, relative risk. ^aModel 1 indicates adjusted for age and sex. ^bModel 2 indicates adjusted for age, sex, body mass index, NIHSS score, hypertension, diabetes, hyperlipidemia, current smoker, brain atrophy, infarction diameter >15 mm and days from stroke onset to admission (blood sampling). *Indicates $P < 0.05$.

results might suggest completely different mechanism compared with EPVS in CS and BG still awaits further studies.

The limitation of our study is that the two serum markers of endothelium activation were only measured at a single time point at baseline with limited sample size. To further determine the pathogenesis of EPVS in lacunar infarction, studies would benefit from both larger sample size and more time sections.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

The following supplementary material is available for this article:

Figure S1. Flow chart for this study.