Lipid Levels Are Regionally Associated with Cerebral Microbleeds in Patients with Intracerebral Hemorrhage

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Background: Lipid levels may be involved in intracerebral hemorrhage (ICH) etiology, which suggested that lipid levels may be associated with the etiology of microbleeds (MBs) in patients with ICH. To explore this, we examined the association between lipid levels and MBs in different cerebral regions in patients with ICH. *Methods:* Patients admitted to our hospital with ICH were consecutively and prospectively included. Demographic and clinical information were collected and analyzed according to the occurrence and location of MBs and levels of triglycerides (TGs). *Results:* Of the 77 patients included in our study, 63 (81.8%) were found to have MBs. Prevalence of MBs in the "deep or infratentorial" region and any region increased with increasing tercile in TG concentration; however, no such trend was observed for strictly lobar MBs. The odds ratio (OR) for occurrence of MBs in deep or infratentorial region was even higher for the third tercile relative to the first: 6.77 (95% confidence interval [CI] 1.31-34.96). The OR for occurrence of MB in any region was even higher for the third tercile relative to the first: 12.24 (95% CI 1.40-106.83). However, the OR for occurrence of deep or infratentorial region and any region in the second tercile relative to the first tercile did not reach significance. Moreover, TG levels did not appear to be associated with the occurrence of strictly lobar MBs. *Conclusions:* High TGs were associated with deep or infratentorial and any MBs but not with lobar MBs. This finding may shed light on the role of lipids in MB and ICH etiology. **Key Words:** Lipid levels—triglyceride—microbleeds—intracerebral hemorrhage.

Introduction

Intracerebral hemorrhage (ICH) in a lobar location is associated with cerebral amyloid angiopathy, whereas ICH in the basal ganglia, cerebellum, or pons is attributed mainly to hypertension or atherosclerotic microangiopathy.[1] Different factors contribute to ICH occurrence in different locations of the brain, suggesting different etiologies. Recent work suggests that lipid levels may be involved in ICH etiology,[2] raising the question of whether they are involved in ICH at all locations or only at certain ones.

Microbleeds (MBs) tend to occur in advance of ICH, suggesting that they are an early stage of the same disease.[3] MBs are pathologic deposits of hemosiderin caused by minor blood extravasation from lipohyalinized small arterioles. If lipid levels are, indeed, involved in the etiology of ICH, they may also be involved in MBs. Therefore,

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analyzing whether lipid levels are associated with MBs, in particular brain locations, may reveal whether the same is true for ICH.

In this prospective study, we investigated the prevalence and location of MBs in a population of patients with ICH. We examined whether lipid levels correlated with MB occurrence and location.

Subjects and Methods

Patients and Evaluation

Patients with spontaneous ICH were prospectively and consecutively enrolled after being admitted to West China Hospital, Sichuan University, Chengdu, China, between May 1, 2012, and March 31, 2013. Spontaneous ICH was defined as intraparenchymal hemorrhage or intraventricular hemorrhage not caused by trauma, brain tumor, or hemorrhagic transformation of arterial ischemic stroke or established pathogenesis, that is, arteriovenous malformation, head trauma, or cavernous angioma. Patients were also excluded if they did not undergo susceptibility-weighted imaging (SWI) or if lipoprotein analysis data were unavailable.

Baseline Data Collection and Categorization

Baseline information was collected at admission on age, gender, and stroke risk factors (hypertension, diabetes mellitus, current smoking, alcohol intake). Cerebral MBs were defined as homogeneous, round focal areas observed throughout the brain, with a diameter less than 10 mm and very low signal intensity on SWI. Cerebral locations of MBs were categorized as either strictly lobar or as "deep or infratentorial." Patients with 1 or more MBs restricted to a lobar location were defined as having strictly lobar MBs. Persons without lobar MBs and with MBs in a deep or infratentorial location were defined as having deep or infratentorial MBs. The presence and location of MBs on SWI was determined independently by 2 neurologists (inter-rater reliability $k = .82$) blinded to clinical data. In case of disagreement, a third neurologist was consulted, and a consensus decision was reached.

Statistical Analysis

The χ^2 or Fisher exact tests were used to assess the significance of differences in categorical variables. The Mann–Whitney U test was used to assess the significance of differences in continuous variables. When appropriate, results were reported as an odds ratio (OR) and 95% confidence interval (CI). Two-sided values of P less than .05 were considered statistically significant. All statistical analyses were performed using SPSS version 16 (IBM, USA). Logistic regression modeling was used to identify variables associated with MB occurrence and location.

Results

A total of 105 consecutive patients were assessed for inclusion in the study, but 21 (20.0%) were excluded because of established pathologies and 6 (5.7%) because of missing data on lipid levels. Of 77 patients included in the final analysis, 54 (70.1%) were men, and mean age at stroke onset was 61.06 ± 12.96 years. Fifty-five patients had supratentorial ICH, 22 patients had infratentorial ICH, 9 patients had thalamic ICH, 33 patients had putaminal ICH, 2 patients had external capsule, and 11 patients had lobar ICH. A total of 63 patients (81.8%) had MBs. Baseline characteristics of patients with ICH are shown in Table 1 according to whether they had MBs. Patients with MBs were more likely to be older and to have higher triglyceride (TG) levels. Then, we examined that which risk factor influenced the MB lesion development in the ICH by univariate logistic regression analysis. Logistic regression identified increasing tercile in TG concentration as an independent marker of MBs lesions ($P = .013$, OR = 2.86, 95% CI 1.25-6.58).

The data were analyzed to determine whether TG levels were associated with particular demographic or clinical variables or with the occurrence and location of cerebral MBs. Triglyceride levels were not associated with demographic variables or risk factors or with the occurrence of strictly lobar MBs. There was a significant trend toward more occurrence of MBs in deep or infratentorial region ($P = .04$) and any region ($P = .03$) with increasing TG tercile (Table 2); however, no such trend was observed for strictly lobar MBs.

Post hoc analysis showed occurrence of MBs in deep or infratentorial region rate to be significantly higher in the third tercile (37.0%) than in the first tercile ($P = .014$). In contrast, occurrence of MBs in deep or infratentorial region rate in the second tercile (28.0%) was not significantly different from those in the first (8.0%; $P = .069$). The OR for occurrence of MBs in deep or infratentorial region was even higher for the third tercile relative to the first: 6.77 (95% CI 1.31-34.96). The OR for occurrence of deep or infratentorial region in the second tercile relative to the first tercile was 4.47 (95% CI .83-24.19).

Moreover, the rate of MBs in any region was significantly higher in the third tercile (96.3%) than in the first tercile (68.0%, $P = .008$). Rate of MBs in any region was not significant between the second tercile (76.0%) and the first (68.0%, $P = .29$). The OR for MBs in any region in the second tercile relative to the first tercile was 1.78 (95% CI .49-6.53). The OR was significantly higher for the third tercile relative to the first: 12.24 (95% CI 1.40-106.83).

Discussion

In this prospective study of patients with ICH, we found that 82% had MBs, consistent with the idea that MBs are strongly associated with ICH and may represent an early stage of the disease. In addition, we