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Original Article

Correlation between biochemical indicators of blood lipid with cerebral vascular diseases

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Abstract: Objective: The objective of this study was to investigate correlation of the changes in serum levels of cholesterol (chol), lipoprotein (a) (Lpa) and homocysteine (HCY) with incident cerebral infarction and cerebral hemorrhage. Methods: Data on a total of 418 patients (318 cerebral infarction events and 100 cerebral hemorrhage cases) were analyzed in this study. Serum chol and HCY levels were tested by means of GPO-PAP. Serum Lpa levels were measured using latex agglutination turbidimetry. Results: Patients with cerebral infarction showed significantly higher serum Lpa levels and anomaly ratio than those with cerebral hemorrhage ($P < 0.05$), while no significant changes were identified for chol and HCY ($P > 0.05$). Analyses by age indicated substantially increased Lpa concentration among cerebral infarction patients > 60 years of age ($P < 0.05$). No statistical significance was observed in other analyses carried out in the study. Conclusion: These results demonstrate that Lpa concentration is clearly correlated with cerebral infarction incidence. Lpa may act as an independent risk factor and could be used as a biomarker for this disease.

Keywords: Cerebral infarction, cerebral hemorrhage, lipoprotein (a), cholesterol, homocysteine

Introduction

Various biochemical indicators of blood lipid have been the focus of extensive research in recent years, including cholesterol (abbreviated as chol thereafter), apolipoprotein A (abbreviated as LPa thereafter) and homocysteine (abbreviated as HCY thereafter). Several lines of evidence have demonstrated that the changes in serum chol, Lpa and HCY levels play a central role in the pathogenesis of atherosclerosis [1, 2]. However, there are sparse data concerning the correlation of these indicators with incident cerebral infarction, and cerebral hemorrhage. Most importantly, the observations documented in existing studies addressing the association of interest have been largely inconsistent.

In the present work, we analyzed data derived from a total of 418 patients composed of 318 cerebral infarction patients and 100 cerebral hemorrhage patients, with an aim to investigate the association of chol, Lpa and HCY with cerebrovascular diseases by testing the alternations in serum levels, thus facilitating early detection and treatment.

Materials and methods

Study population

We identified a total of 418 patients with cerebrovascular diseases (318 cerebral infarction patients, 100 cerebral hemorrhage patients) from a consecutive series of inpatients presenting at 161 Hospital of PLA (Internal Medicine department and Neurosurgery Department), from April 2013 through June 2014. There were 193 men and 225 women. The mean age was 62.3 ± 11.5 years (range 39-86 years). Diagnosis of either cerebral infarction or cerebral hemorrhage was in accord with international standard definitions. Patients with each disease were categorized as younger group (≤ 60 year) and elderly group (> 60 years). All study subjects provided written, informed consent. Ethical approval was granted by local ethics committees.

Methods

3.5 mL venous blood was collected from each participant using vacuum blood tubes. Serums were isolated by Hitachi H7600 automatic bio-

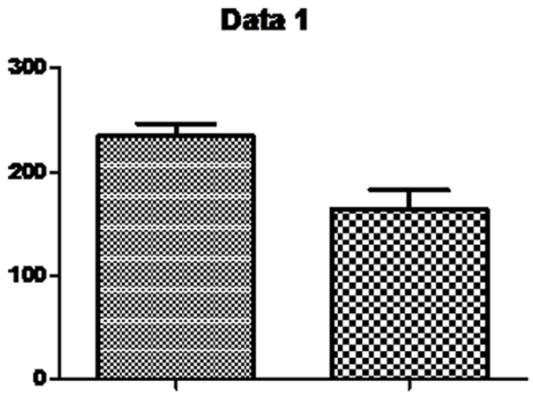

Figure 1. Serum Lpa levels among cerebral infarction and cerebral hemorrhage patients.

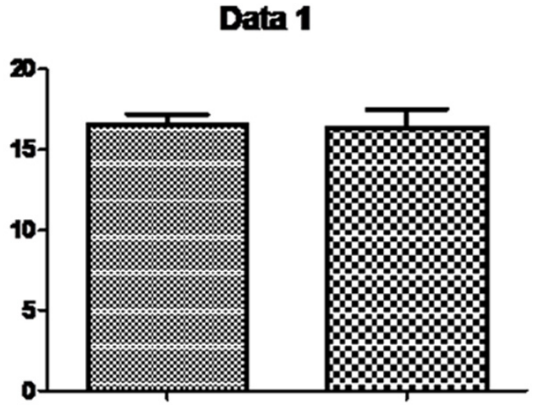

Figure 2. Serum HCY levels among cerebral infarction and cerebral hemorrhage patients.

chemical analyzer. Serum chol and HCY levels were tested by means of GPO-PAP using Water kits and Zhongyuan Biological kit, respectively. Serum Lpa levels were determined by latex agglutination turbidimetry using water kits. Diagnostic criterion for HCY was > 15 mol/L.

Statistical methods

Data were shown as X ± s. Statistical analyses were done with the SPSS16.0 statistical software. Difference between groups in serum levels was compared using the chi square test. A *P* value below 0.05 was taken as the significance threshold.

Results

Serum levels of Lpa, HCY and chol

We found a statistically significantly increased serum Lpa levels among patients sustaining

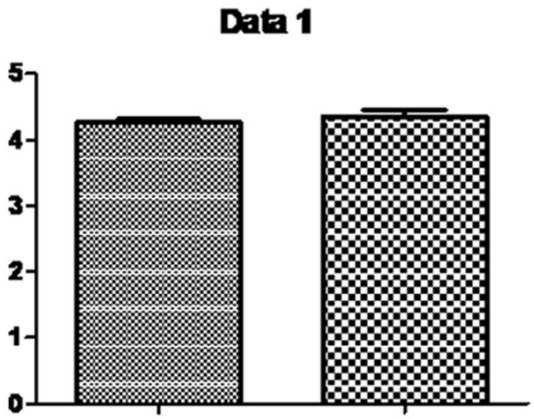

Figure 3. Serum chol levels among cerebral infarction and cerebral hemorrhage patients.

cerebral infarction as compared to the patients with cerebral hemorrhage (220.57 ± 12.36 vs. 160.84 ± 17.98, *P* = 0.004) (see **Figure 1**). However, no significant changes in serum levels were observed for HCY and chol levels when data derived from cerebral infarction patients were compared to those from cerebral hemorrhage patients (16.53 ± 10.98 vs. 16.3 ± 10.98, *P* = 0.993; 4.34 ± 0.95 vs. 4.02 ± 0.94, *P* = 0.863, respectively). The results were illustrated in **Figures 2** and **3**, respectively.

Anomaly ratio

Lpa > 300 mg/L, HCY > 15 μmoL/L and CHOL > 5.69 mmoL/L were set as the standards for anomaly judgment. As shown in **Table 1**, the anomaly ratio of Lpa in cerebral infarction group and cerebral hemorrhage group was 30.1% and 14%, respectively, with the X^2 test showing a significantly increased ratio in the former group (*P* = 0.003). We then tested the ratio for HCY and found no statistical difference between the investigated groups (cerebral infarction group vs. cerebral hemorrhage group: 42.1% vs. 40%, *P* > 0.05). In addition, we identified that the anomaly ratio of chol in cerebral infarction group and cerebral hemorrhage group was 3.7% and 6.2%, respectively. We did not test the statistical difference due to low positive rate.

Serum levels of Lpa, HCY and chol in different age groups

Among the patients with cerebral infarction, we found that the serum Lpa levels were substan-

Table 1. Positive rate of LPa and HCY in patients with cerebral vascular diseases

Groups	n	LPa		HCY	
		n	Rate	n	Rate
Cerebral infarction	318	96	30.1%	134	42.1%
Cerebral hemorrhage	100	14	14%	40	40%

Table 2. Comparisons between different age groups in the content of parameters tested

Groups	n	Parameters tested		
		HCY	LPa	Cholesterol
Cerebral infarction				
≤ 60 years of age	105	16.37 ± 9.6	193.2 ± 16.7	4.52 ± 1.02
> 60 years of age	213	16.52 ± 13.4	254.2 ± 16.34	4.14 ± 0.93
P		0.145	0.01	0.25
Cerebral hemorrhage				
≤ 60 years of age	47	15.4 ± 9.72	149.2 ± 15.7	4.4 ± 0.97
> 60 years of age	53	17.11 ± 10.74	179.8 ± 16.2	4.3 ± 0.77
P		0.332	0.91	0.19

tially higher in the elderly group as compared to the younger group ($P = 0.01$). In contrast, we did not find any statistical significance in terms of HCY and chol. The insignificant results remained when the serum levels of the three biochemical indicators were compared between the two groups sustaining cerebral hemorrhage (see **Table 2**).

Discussion

It is widely acceptable that the development of atherosclerosis can be accelerated as a result of VLDL and LDL in high concentrations transporting triglyceride and cholesterol into the peripheral blood vessels. An increasing body of literature has firmly established that formation and progression of cerebrovascular diseases are significantly associated with a variety of conditions, including total cholesterol, triglyceride, high density lipoprotein, low density lipoprotein, lipoprotein A and other lipids [3-6].

Lpas are lipoprotein particles formed as a result of the combination of low density lipoprotein, apolipoprotein B100 and Lpa through disulfide bonds [1]. They are a class of independent proteins and remain unaltered when changes occurred in chol, low density lipoprotein, and triglyceride. Known features of Lpa are to exert effects on the functions of plasminogen in vivo, promote blood clot formation, and help low density lipoproteins adhere to the artery wall, thereby promoting plaque formation and ultimately atherosclerosis and stenosis. It is therefore conceivable that increased content of Lpa is linked with the occurrence of cerebralvascular diseases. According to Carey et al., Lpa induces coronary heart disease and cerebral infarction by promoting atherosclerosis and thrombosis [7]. Here we have found that Lpa concentration is significantly higher among patients with cerebral infarction than those with cerebral hemorrhage. The statistical significance persisted when anomaly ratio was tested. These data suggest that cerebral infarction incidence is clearly associated with increased Lpa concentration. In terms of the association of Lpa concentration with cerebral hemorrhage, previous reports have produced inconsistent results. For example, Woo et al. conducted a case-control study and found significantly higher serum levels among patients [8]. In contrast to the previous observation, Deng et al. failed to identify any statistical significance [9]. Also, Ma et al. reported that both cerebral infarction patients and cerebral hemorrhage patients showed increased levels; the increase, however, did not reach the statistical significance [10]. Interestingly, Oliveira et al. performed immune turbidimetry to detect the serum Lpa levels among health college students, finding no linkage between the serum levels and gender [11]. We herein found that Lpa concentration was significantly lower in cerebral hemorrhage patients than in cerebral infarction patients. This observed statistical significance merits further investigation due to sample insufficiency and different disease severity. We additionally found substantially higher Lpa concentration among cerebral infarction patients > 60 years of age. However, no noteworthy differences were observed in cerebral hemorrhage patients. These results seem to point to the possibility that Lpa may have an impact on cerebral infarction, especially the elderly patients.

HCY are natural products of the human metabolism and have substantial physiological significance [12]. Evidence is mounting that HCY associated with atherosclerosis is a risk factor for cardiovascular and cerebrovascular diseases, such as coronary heart disease and stroke [13]. Its role in cardiovascular and cerebrovascular events is mainly ascribed to the engagement in thrombogenesis, responses to oxidative stress and endothelial dysfunction. Schaffer et al. investigated 3056 patients undergoing angiography (diagnosis standard, lockage of > 50% vessel) and measured the concentration after fasting, suggesting that high levels of HCY are markedly associated with age and gender and may act as an independent risk factor for coronary heart disease [14]. Bhargava et al. employed 167 patients with vascular occlusion of coronary heart disease, consisting of 43 coronary heart events, 82 cerebral vascular events, and 42 peripheral vascular, and concluded that anomaly ratio remarkably increased in the former two groups [15]. An experimental study of 60 cerebral infarction patients suggested that both serum HCY levels and anomaly ratio are notably higher relative to the control group and the investigators stated that there is a clear association of HCY with cerebral infarction [16]. Conversely, the results of this study showed no significant difference in either concentration or anomaly ratio for HCY and chol among patients with cerebral infarction or cerebral hemorrhage and no relationship of the two indicators to age. Possible reasons for the considerable inconsistency include sampling variance and different study designs. In this study, we investigated the serums levels only in patients and the results could merely be interpreted in diseases. It is also possible that serum HCY levels are indeed correlated with the two diseases, which requires being confirmed in future studies.

Total chol refers to all lipoprotein chols in the blood, including free chol and chol ester, with the liver being the main organ responsible for their synthesis and storage. Accumulated data have shown that high levels of triglycerides and total cholesterol are important risk factors inducing atherosclerosis and cerebrovascular diseases [17, 18]. Triglyceride and total cholesterol are transported from the liver into peripheral vessels through VLDL. Existing studies have indicated that VLDL vaccination enhances neonatal tolerance, thus protecting the epithelial cells from lipid deposition [19]. It is also suggested that chol content is related to carotid artery intima thickness in response to artery stenosis [20]. High chol was also described in a case-control study of stroke patients [21]. Further evidence was provided by Scigliano et al., who found that patients previously treated with levodopa had lower lipid content than the untreated patients, indicating that levodopa has a major impact in altering human lipid content [22]. Nevertheless, wide discrepancy has been shown in published studies [22-25]. Mustanoja et al. reported that in principle chol exists in the membrane, and the low levels of chol reduces the capability of vessels in defense against rupture, and consequently increases the mortality of cerebral hemorrhage [26].

In conclusion, we have shown that plasma levels of Lpa in cerebral infarction patients are significantly higher than those observed in cerebral hemorrhage patients. This suggests that Lpa is a potential independent risk factor for cerebral infarction and acts as a useful biomarker for the disease, an observation consistent with many previous studies.

Disclosure of conflict of interest

None.

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