Apolipoprotein levels in acute cerebral infarction are correlated with TOAST subtypes

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Abstract

Objective: To determine the association of apolipoprotein levels with acute cerebral infarction (ACI) and the clinical significance of this association. Method: The apolipoprotein B (ApoB), apolipoprotein A1(ApoA1), the apoB/apoA1 ratio and general characteristics of 168 patients with ACI and TOAST (Trail of Org 10172 in Acute Stroke Treatment) subtypes) and 86 healthy people were analyzed. Result: The ratio of ApoB/ApoA1 in ACI patients was significantly higher compared with that of healthy controls ($p<0.01$). The level of ApoB and the ApoB/ApoA1 ratio in patients with cardio-embolism (CE), large artery atherosclerosis (LAA), and small artery occlusion (SAO) were significantly higher than the other subtypes ($p<0.05$). Additionally, the level of ApoA1 was significantly lower in the LAA group compared with the other subtypes ($p<0.05$). The levels of ApoB, ApoA1 and ApoB/ApoA1 ratio were not significantly different for patients with stroke of other determined etiology (SOD) or stroke of other undetermined etiology (SUE). The severity and prognosis of TOAST subtypes (5 groups) was significantly different ($p=0.034$), and presented a correlation with the subtypes (TOAST criteria) of cerebral infarction. Conclusion: Our study showed that the levels of ApoB, ApoA1 and the ApoB/ApoA1 ratio were different in ACI patients with different TOAST subtypes and these indicators may have clinical significance for ACI patients, including early diagnosis, prevention, treatment and prediction of prognosis.

Keywords

Acute cerebral infarction, apolipoprotein, TOAST, ratio.

1. Introduction

Apolipoproteins play a significant physiological role in the metabolism of lipoproteins. There are 6 classes of apolipoproteins, which differ in biological function. Apolipoprotein A1 (ApoA1) is the major component of high-density lipoprotein cholesterol (HDL-CHOL). Apolipoprotein B (ApoB) binds with chylomicrons and low-density lipoprotein cholesterol (LDL-CHOL), making up 97% of the total protein in LDL-CHOL. Therefore, the levels of ApoA1 and ApoB directly reflect the levels of HDL-CHOL and LDL-CHOL [1].

ACI is caused by different causes and pathological mechanisms and the risk factors of different ischemic stroke etiology may also be different.

TOAST criteria is a multicenter, randomized, controlled study to observe the safety and efficacy of low molecular weight heparin (Org10172) in the treatment of ACI,It pays great attention to the classification of the etiology of ischemic cerebrovascular disease ,has good reliability in clinical application ,important reference value and guiding significance for reducing the incidence, mortality and disability rate of stroke.

The primary consequence of atherosclerosis is the membrane destruction of the interior arterial wall In severe cases, the atherosclerosis involves The intermediate membrane and can cause the accumulation of cholesterol ester on the arterial wall to form atherosclerotic plaque , a pathological

change of thickness and stenosis of the vessel wall fiber. ApoA1 and ApoB are respectively considered an atherosclerosis protective factor and a risk factor. The ratio of these two proteins has significant diagnostic and preventive value as indicators of atherosclerosis and cardiovascular disease, and the ApoB/ApoA1 ratio higher than 0.9 indicates risk of Cardio-cerebrovascular diseases [1], This result is consistent with the results of this paper..The ApoB/ApoA1 ratio is of more clinical significance than the individual amounts of ApoA1 or ApoB.

This study was performed to compare the serum levels of apolipoprotein among different subtypes of acute cerebral infarction and control subjects to analyze whether the levels of apolipoproteins can be used as a predictor of acute cerebral infarction. to understand the characteristics of ApoB/ApoA1 ratio in different TOAST subtypes is helpful for choosing the appropriate treatment and preventive measures

2. Materials and methods

2.1 Subjects

The study group consisted of 168 patients with ACI admitted to the Neurology Department of our hospital between March 2013 and November 2015. The subjects were classified by stroke subtype using TOAST etiological classifications for cerebral infraction. The groups were patients with large artery atherosclerosis (LAA), cardio-embolism (CE), small artery occlusion (SAO), stroke of other determined etiology (SOD) or stroke of other undetermined etiology (SUE). The subjects included 102 males (60.7%) and 66 females (39.3%) aged from 40-81 years with an average age of (59.6±14.55) years and onset time within 72h. All the patients conformed to the diagnostic criteria modified by the 4th National Academic Conference of Cerebrovascular Disease and were confirmed after CT and/or MRI examinations. Subjects in the control group were 86 healthy people including 45 males (52.3%) and 41 females (47.7%) who underwent a routine physical examination. The ages ranged from 31-81 years and the patients had no history of cerebral infarction. Head CT or MRI confirmed the absence of cerebral infarction; head magnetic resonance angiography or neck CT angiography confirmed the absence of cerebral vascular disease.

2.2 Method

The relevant indicators in the ACI group and the control group were compared using the past medical history, personal history, and clinical and laboratory reports. Examinations were performed including ECG, cardiac ultrasound, Doppler ultrasonography, cerebral CT, MRI, and MRA, head CT angiography (CTA), or whole-head digital subtraction angiography (DSA) for subjects in the cerebral infraction groups. TOAST classification of etiology was performed, and the inconsistently classified types were revised after discussion. Identical information was recorded for all the subjects enrolled to the control group except for imaging examination results.

Determination method

Fasting venous blood 3ml was extracted from all the patients within 72h after symptom onset and the ApoA1 and ApoB levels were measured with an automatic biochemical analyzer. The severity of the 168 cases of ACI was classified as 3 types. Light: 69 cases; conscious, paralyzed muscle strength of III ~ IV level; mild: 47 cases, conscious, paralyzed muscle strength of I ~ II level; severe: 52 cases with disorder of consciousness or with paralyzed muscle strength of 0.

Statistical method

The data were summarized as the means ± standard deviation (SD) for continuous variables and as frequencies and percentages for categorical variables. One-way ANOVA and chi-square test were used to compare the differences between the groups for the continuous and categorical variables, respectively. Bonferroni method was used for multiple comparisons. p-values lower than 0.05 were considered statistically significant. The statistical analysis was made using the Statistical Package for the Social Sciences (SPSS) Statistics software - version 20.0 (IBM, US).

3. Results

3.1 Comparison of general characteristics in ACI patients of different TOAST subtypes (Table 1).

The 168 ACI patients were composed of 21 (12.5%) CE group, 47 (28%) LAA group, 66 (39.3%) SAO group, 15 (8.9%) SOE group and 19 (11.3%) SUE group. The occurrence of ischemic heart disease (IHD) in CE group was higher than that in the other groups ($p<0.05$); age, gender, diabetes, hypertension, etc. presented no statistical significance in each subtype ($p>0.05$).

Table 1. Comparison of general conditions in ACI patients of different TOAST subtypes

	CE group	LAA group	SAO group	SOD group	SUE group
Case amount	21 (12.5%)	47 (28%)	66 (39.3%)	15 (8.9%)	19 (11.3%)
Age (years, $\bar{x}\pm s$)	62.8±15.9	57.5±13.2	59.4±12.9	60.5±15.1	61.3±12.3
Amount of male cases	13 (61.9%)	31 (66%)	39 (59.1%)	9 (60%)	10 (52.6%)
Amount of hypertension cases	13 (65.2%)	29 (61.7%)	42 (63.6%)	9 (60%)	9 (47.4%)
Amount of diabetes cases	8 (38.1%)	16 (34.1%)	23 (34.8%)	7 (46.7%)	7 (36.8%)
Amount of IHD cases	159 (65.2%)*	8 (15.7%)	13 (19.69%)	1 (6.67%)	2 (10.53%)

* The differences have statistical significance when $p<0.05$.

3.2 Comparison of Apo levels and the ApoB/ApoA1 ratio in the ACI group and the control group (Table 2).

Table 2. Comparison of Apo levels in ACI group and the control group

Groups	Case number	ApoA1(g/L)	ApoB(g/L)	ApoB/ApoA1(g/L)
Cerebral infarction	168	1.12±0.25	0.82±0.28	0.72±0.30
Control group	86	1.27±0.28	0.70±0.30	0.56±0.26
p value		0.026	0.002	<0.001

* The differences have statistical significance when $p<0.05$.

The level of ApoB in the ACI group was significantly increased relative to the control group ($p<0.05$). ApoA1 was significantly reduced than the levels of the control group ($p<0.05$). The ApoB/ApoA1 ratio was significantly higher than that of the control group ($p<0.05$).

3.3 Comparison of Apo levels in TOAST subtypes of ACI patients and the control group (Table 3).

ApoB levels were significantly higher in CE, LAA and SAO groups compared to the control group ($p<0.05$). The ApoA1 levels were not significant different between the ACI subtypes and the control group. When ACI occurred, the ratios of ApoB/ApoA1 in CE, LAA and SAO groups were significantly higher than that of the control group ($p<0.05$).

Table 3. Comparison of Apo levels in TOAST subtypes of ACI patients and the control group

	n	ApoA1(g/L)	p value	ApoB(g/L)	p value	ApoB/ApoA1(g/L)	p value
Control group	86	1.27±0.28	0.125a	0.70±0.30	0.016a	0.56±0.26	0.002a
CE group	21	1.19±0.18		0.88±0.32	0.151	0.76±0.33	0.078
LAA group	47	1.15±0.25		0.82±0.26	0.299	0.74±0.28	0.01
SAO group	66	1.23±0.27		0.84±0.30	0.033	0.72±0.32	0.011
SOD group	15	1.27±0.21		0.79±0.28	1	0.64±0.21	1
SUE group	19	1.15±0.26		0.73±0.27	1	0.66±0.30	1

a. The first line of pvalue for one-way-ANOVA method. The results are data of six groups and the others for the results of Bonferroni multiple comparisons results.

3.4 Comparison of ApoB/ApoA1 levels in acute cerebral infarction patients with TOAST subtypes (Table 4).

The severity and prognosis of TOAST subtypes (5 groups) was significantly different (p=0.034), and presented certain correlation with the subtypes (TOAST criteria) of cerebral infarction.

Table 4. Comparison of ApoB/ApoA1 levels in ACI patients with TOAST subtype

	ApoB/ApoA1	Clinical severity			prognosis		
		Light	Mild	Severe	Cure	Improved	Death
CE group (n=21)	0.76±0.33	5 (23.81%)	7 (33.33%)	9(42.86%)	6 (28.56%)	13 (61.91%)	2 (9.53%)
LAA group (n=47)	0.74±0.28	5 (10.64%)	12 (25.53%)	30 (63.83%)*	8 (17.02%)	36 (76.60%)	3 (6.38%)
SAO group (n=66)	0.72±0.32	42 (63.63%)	19 (28.79%)	5 (7.58%)	29 (43.94%)	37 (56.06%)	0
SOE group (n=15)	0.64±0.21	7 (46.67%)	6 (40.00%)	2 (13.33%)	5 (33.33%)	10 (66.67%)	0
SUE group (n=19)	0.66±0.30	10 (52.63%)	3 (15.79%)	6 (31.58%)	6 (31.58%)	12 (63.16%)	1(5.26%)

* The differences have statistical significance when $p<0.05$.

4. Discussion

Cerebrovascular disease is one of the three major deadly diseases and the primary cause of disability in China. The primary consequence of atherosclerosis is the membrane destruction of interior arterial wall, while the intermediate membrane involved in serious cases can cause the massive accumulation of cholesterol ester on the arterial wall to form atherosclerotic plaque. Lipid metabolism disorder is the major indicator seen in clinical practice. LDL-C and HDL-C are additional indicators for clinical practice that have become used recently. Blood cholesterol can be greatly affected by diet, physical activities and other factors, but the apolipoprotein that transports lipids into and out of the artery wall are not affected by diet, so the level of apolipoprotein may be more meaningful than other indicators for the prediction of atherosclerotic cardiovascular disease [2, 3]. Studies have shown that lipid metabolism disorder is actually caused by the metabolism disorder of apolipoprotein and the occurrence of cerebral infarction (especially Apolipoprotein metabolism disorders) [4]. Zhuang Yiyi et al. [1] suggested that ApoA1 may be a better indicator than LDL-C, TC, HDL-C, TG and others indicators for predicting the risks of atherosclerotic cardiovascular events. O'Donnell MJ et al. [5] also reported that decreased ApoA1 levels are significantly associated with the risks of cerebral infarction.

ApoB is the major apolipoprotein component of LDL-C and VLDL. It promotes the proliferation of arterial smooth muscle cells as well as their entrance to the sub-layer of endomembrane, the primary trigger factor inducing atherosclerosis. ApoB also promotes the formation of foam cells and

stimulates the esterification of cholesterol inside macrophages, and thus induces atherosclerosis [6]. Xing Zhiqiang et al. [7] divided patients with cerebral infarction into mild, moderate and severe groups and found that ApoB levels were positively correlated with the clinical severity of stroke, suggesting that ApoB level may be the risk factor for cerebral infarction. In accordance with previous reports, the ApoB was positively correlated with the inhibitor of plasminogen activation [8], suggesting that ApoB may also play a role in the occurrence of ACI by inhibiting the activity of the fibrinolytic system.

As the major Apo lipoprotein component of HDL-C, ApoA1 not only participates in the reverse transport of TC and regulation of lipid metabolism, but also functions as a negative phase protein with anti-inflammatory action. It acts on multiple steps of the inflammatory process, protects arteries, and thereby inhibits the development of atherosclerosis. There may be three mechanisms of atherosclerosis induced by low ApoA1 in patients with cerebral apoplexy: (1) Navab et al. [9] proposed that ApoA1 inhibits the oxidation of LDL, so lower amounts of ApoA1 would result in higher oxidation of LDL. (2) ApoA1 participates in the activation of lecithin-cholesterol acyl transferase (LCAT) and is capable of promoting reverse cholesterol transport, transporting cholesterol from peripheral tissues to the liver. This reduces the amount of cholesterol in peripheral tissue cells, reducing cholesterol deposition in these cells, and reducing the morbidity risk of atherosclerosis. (3) Low ApoA1 levels has been linked to the aggravation of systemic inflammatory response syndrome [10]. The binding of ApoA1 with HDL obstructs the contact between cells, inhibits the activation of monocytes and the production of inflammatory cytokines [11] and therefore ApoA1-HDL acts as a natural inhibitor of lymphocytes and monocytes. Thus, reduced ApoA1 results in the loss of this inhibitory effect and favors the development of atherosclerosis.

The ApoB/ApoA1 ratio represents a balance between two particles with different functions. The balance between ApoB and ApoA1 is correlated with the occurrence of cardiovascular disease [3] and ApoB/ApoA1 is positively correlated with cerebral infarction in patients over 70 years and may be an independent risk factor of cerebrovascular disease [12]. Wang Huqing et al. [13] demonstrated that the ApoA1 levels and the ApoA1/ApoB ratio in ACI group decreased significantly while the ApoB levels increased significantly. Kim SJ et al. [14] found that the ApoB/ApoA1 ratio may predict asymptomatic carotid stenosis, where the higher ratio indicates a greater risk. Walldius et al. [15] also proposed that the ApoB/ApoA1 ratio was a strong predictive factor for cardiovascular and cerebrovascular events with more significance than separate measurement of ApoA1 or ApoB. Additionally, the ApoB/ApoA1 ratio is a greater predictor than the ratio of LDL and HDL and may be a better indicator of cholesterol balance than lipids, lipoproteins and cholesterol ratios [16].

Relevant reports [6] indicated the priority of ApoB/ApoA1 ratio over conventional lipid markers in the prediction of cardiovascular diseases. The ApoB level reflects the total amount of lipoprotein particles inducing atherosclerosis and the ApoA1 level reflects the total amount of HDL particles resisting atherosclerosis, and thus together they more accurately reflect the risks of cardiovascular events compared to HDL, LDL and other conventional serum lipid indicators. In studies of factors to allow prediction of coronary artery disease, a prospective study about apolipoprotein-related mortality indicated that the ApoB/ApoA1 ratio was more informative than other cholesterol ratios, including CHOL/HDL, LDL/HDL and NON-HDL/HDL [12]. Other studies found that the diurnal variation coefficient of ApoB/ApoA1 is very low, <2%, greatly enhancing the use of this as a laboratory tool. In addition, ApoB/ApA1 measurement does not require fasting or have strict sampling time requirements [2].

As a major structural component of lipoproteins, the apolipoprotein participates in the lipid metabolism of the organism. The change of serum apolipoprotein levels affects the extent of atherosclerosis. In comparison with the control group, the levels of ApoA1 and ApoB in the ACI group of this study were significantly different.

After TOAST classification, we found that ApoB levels and the ApoB/ApoA1 ratio in the three groups (CE, LAA, SAO) of ACI atherosclerosis were significantly higher than that in the control

group, while the ApoA1 level in the LAA group was significantly lower than that in the control group. The results indicated that patients with increased ApoB levels and/or reduced ApoA1 levels in these three groups were more likely to experience cerebral ischemic events, consistent with the lipoprotein-related conclusions. This suggested that changes in apolipoprotein levels were closely related to ACI, especially atherosclerotic cerebral infarction, and may be associated with disease severity. The levels of ApoB and ApoB/ApoA1 ratio were significantly higher in the SAO CE, and LAA groups and the levels of ApoA1 in the LAA and SUE groups were lower than that in the control group. This indicates that apolipoprotein disorders were not only correlated with the occurrence of ACI, but also were related to the TOAST etiology classifications. Measuring the levels of serum ApoB/ApoA1 ratio in ACI patients may be more beneficial to the understanding of the lipid disorders than measurement of other lipid indicators to improve diagnosis, prevention, treatment, and prognosis.

5. Conclusion

Our results showed that the levels of ApoB, ApoA1 and the ApoB/ApoA1 ratio were different in ACI patients with different TOAST subtypes. These indicators may have clinical significance for ACI patients and could promote early diagnosis, and facilitate the prevention and treatment of the disease and allow the development of more accurate prognosis.

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References

[1] Ye Guiyun, Hu Wangping, Chi Xidi, et al. Apolipoprotein A-1 and b the ratio of value to predict the risk of vascular disease [J]. Journal of Chinese Practical Diagnosis and Therapy, 2012, 4 (4): 26-336.

[2] Hu Qiuyan. The combined detection of in patients with acute cerebral infarction and high density lipoprotein and apolipoprotein B content [J]. Journal of traditional Chinese medicine, 2009, 21 (6): 115-115.

[3] Sun Zhaorui, Chai Xiaowen. 168 patients with cardiovascular and cerebrovascular diseases serum apolipoprotein Al, B result analysis [J]. China Journal of traditional Chinese medicine, 2007, 5 (8): 54-55.

[4] Ridker PM, Rifai N, Cook NR, et al. Non-HDL Cholesterol, apolipoproteins A-I and B100, standard lipid measures, lipid ratios, and CRP as risk factors for cardiovascular disease in women [J]. JAMA, 2005, 294(3): 326-333.

[5] O'Donnell MJ, Xavier D, Liu L ,et al. risk factors for ischemic and intracerebral hemorrhagic stroke in 22 countries(the INTERSTROKE study) : a case-control study [J].Lancet, 2010, 376(9735): 112-123.

[6] Gardener H, Della Morte D, Elkind MS, et al. Lipids and carotid plaque in the Northern Manhattan Study(NOMAS) [J]. BMC Cardiovasc Disord, 2009, 9: 55.

[7] Xing Zhiqiang, Zhao Shizhu. In patients with acute cerebral infarction and clinical significance of detection of apolipoprotein B [J]. Family medicine, utility 2007, 5 (7): 634.

[8] Kostapanos MS, Christogiannis LG, Bika E etal Apolipoprotein B-to-A1 ratio as a predictor of acute ischemic no embolic stroke in elderly subjects [J]. J Stroke Cerebrovasc Dis, 2010, 19(6): 497-502.

[9] Navab M, Anantharamaiah GM，Rsddy ST, et al. The oxidation hypothesis of atherogenesis: the role of oxidized phospholipid and HDL [J]. J Lipid Res, 2004, 45 (6): 993-1007.

[10] Chenaud C, Merlani PG, Roux-Lombard P, et al. Low apolipoprotein AI level at intensive care unit admission and systemic inflammatory response syndrome exacerbation [J]. Crit Care Med, 2004, 32(3): 632-637.

[11] Levisianou D, Melidonis A, Adamopoulou E, et al. Impact of the metabolic syndrome and its components combinations on arterial stiffness in type 2 diabetic men [J]. Int Angiol, 2009, 28 (6) :490－495.
[12] Baena-Diez J M, Berumudez-Chillida N, GariaLareo M, et al. Role of pulse pressure, systolic blood pressure, and diastolic Blood pressure in the prediction of cardiovascular risk [J].. Cohort Study J. Med Clin (Barc), 2008, 130 (10): 361-365.
[13] Wang Huqing, Wu Haiqin, Zhang Lei, et al. (J) Changes in patients with acute cerebral infarction apolipoprotein AI, apolipoprotein B and its ratio [J].. Journal of clinical neurology, 2010, 23 (2): 129-129.
[14] Kim SJ, Song P, Park JH, et al. Biomarkers of asymptomatic carotid stenosis in patients undergoing coronary artery bypass grafting [J]. Stroke, 2011, 42(3): 734-739.
[15] Walldins G, Jungner I. The ApoB /A1 ratio:a strong new risk factor For cardiovascular disease and a target for lipid lowering therapy: A review of the evidence J.J Inter Med, 2006,2(59):493.
[16] Caplan L, Wong KS, Gao S,et al. Is hypoperfusion an important cause of stroke? If so, how? [J] Cerebrovasc Dis, 2006, 21(3):145-153.