ANTI-CARDIOLIPIN ANTIBODIES, NEW RISK FACTORS IN PATIENTS WITH ACUTE CEREBRAL INFARCTION

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Abstract

Bacground: The relationship between serum anti-cardiolipin (aCL) antibody correlates with some risk factors and severity level in patients with cerebral infarction. **Subjects and Methods**: cross-sectional descriptive study, 68 patients with acute cerebral infarction at Hue University Hospital. Data processing method according to usual medical statistics and SPSS 16.0. **Results:** (*1) The proportion of positive and serum antibody levels in patients with acute cerebral infarction:* (i) aCL-IgG antibody (+) accounted for 20.6%; aCL-IgM (+) accounted for 7.4% ; (ii) The average concentration of the aCL-IgG (+) was 33.98 ± 29.42 GPL/mL and aCL-IgM (+) was 26.58 ± 10.30 MPL/mL. (2) *The relationship between the aCL antibody concentration with some associated risk factors and the severity of acute cerebral infarction:* (i) There was a close correlation between aCL-IgG levels ($r = 0.709$; $p < 0.01$); inverse correlation with Glasgow Coma Scale ($r = -0.643$; $p < 0.01$); (ii) There was an average inverse correlation between the concentration of aCL-IgM with size of injury ($r = 0.407$; $p < 0.01$); and average inverse correlation with Glasgow Coma Scale ($r = -0.393$; $p <0.01$)**;** (iii) There was an average inverse correlation between the concentration of IgM aCL-with cholesterol levels ($r = -0.31$ and $p <0.05$) and LDL-C levels ($r = 0.25$ and $p <0.05$); (iv) There was no correlation between the aCL-IgG concentrations with level of lipid profiles; (v) There was no correlation between aCL IgG/IgM concentrations with level of other indicators: glucose, hs-CRP, fibrinogen, urea, creatinine, platelet count, blood pressure of acute cerebral infarction patients. **Conclusion**: aCL antibody of serum was high and correlated with severity of acute cerebral infarction.

Keywords: *anti-cardiolipin antibody (aCL), cerebral infarction*

1. BACKGROUND

Stroke is one of the causes of death in the world, and often get severe sequelae, creating a burden to family and society. In particular, cerebral infarction accounts for 80-85% of stroke. Cerebral infarction is considered as life-threatening diseases as well as a severely handicapped illness, both mentally and physically; thus preventing the risk factors are key strategies for each community and for each individual, in order to limit the frequency of stroke. There have been many previous studies showed that risk factors such as hypertension, dyslipidemia, diabetes, cardiovascular disease, hs-CRP, ... including autoimmune factor, an interested issue in many recent studies. According to the study in the UK, anticardiolipin (aCL) can be considered as an independent prognostic sign for both deaths and clinical sequelae followed by cerebral infarction; and some studies in US also showed the percentage of positive aCL antibodies in patients with cerebral infarction, the frequency of aCL antibodies increased in first time cerebral infarction patients and is an independent risk factor causing cerebral infarction. Understanding this issue may provide new therapeutic targets to improve the outcome of cerebral infarction patients, contributing to the diagnosis, treatment, follow-up, and prognosis. In Vietnam, there is no research on cerebral infarction patients. Stemming from the above problems, we conducted this study with two objectives:

1. To Identify positive rate and the concentration of serum aCL antibodies in patients with acute cerebral infarction.

2. To determine the correlation between aCL antibody concentration with some associated risk factors and the severity of acute cerebral infarction.

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- Received: 30/3/2015; Revised: 27/4/2015; Accepted: 20/5/2015

2. SUBJECTS AND METHODOLOGY

2.1. Subjects

68 patients aged from 18 years, treated at the Internal Medicine Department of Hue University Hospital, from 11/2013 to 6/2014 diagnosed with acute cerebral infarction.

Exclusion criteria:

- Brain Injury, localized paralysis after partial seizures, migraine,...

- The other brain diseases, not acute cerebral infarction, such as: chronic cerebral infarction, subacute cerebral infarction, cerebral hemorrhage, transient stroke, brain tumors, brain abscess,...

- Acute cerebral infarction in patients with cancer, systemic disease,...

2.2. Methodology

Cross-sectional descriptive study.

2.2.1. Clinical examination methods: taking history, physical examination for meticulous selection the research subjects, assessment of risk factors.

Diagnosis of stroke: based on clinical and criteria

* Clinical: based on the WHO definition of stroke.

***** Subclinical**:** computerized tomography brain scans with a density of 20-30 HU in infarcted area.

*** Diagnosis phase: S.Oppenheimer and V.Hachinski.**

Acute phase: ≤1 week; Subacute phase: 2-4 weeks; Chronic Phase: > 4 weeks

Diagnosis the severity of cerebral infarction: based on Glasgow scale, classified according to the degree of brain damage:

Normal: 15 points; Minor:13-14 points; moderate: 9-12 points; Severe: ≤ 8 points

***2.2.2. Methods of functional test*:** computerized tomography brain scans, ECG, chest x-ray, carotid Doppler ultrasound, echocardiography.

***2.3.3. Methods of laboratory tests*:** Quantificate aCL (IgG, IgM), blood count, blood sugar, lipid profile, hs-CRP, fibrinogen, urea, creatinine at the hospital.

- Data processing method according to usual medical statistics and SPSS 16.0.

3. RESULT

3.1. Distribution by age of disease groups

Table 3.1. The average age distribution of patients by sex

Sex	Cerebral infarction		Age				p
	n	%	$\overline{X}$	SD	Minimum	Maximum	
Male	40	**58.8**	66.12	12.85	45	90	> 0.05
Female	28	41.2	68.00	11.24	45	87	
Total	68	100	**66.90**	12.16	45	90	
Male/Female = 1.43							

The mean age of patients was 66.90 ± 12.16 yrs, male was 58.8%, the ratio M/F was 1.43. The average age of men and women were similar with p > 0.05.

3.2. Positive proportion and average serum aCL concentration of patients with acute cerebral infarction

Table 3.2. Positive proportion of aCL in acute cerebral infarction patients

aCL	IgG		IgM	
	n (68)	%	n (68)	%
Positive (>18GPL/MPL)	14	20.6	5	7.4
Negative (<12GPL/MPL)	54	79.4	63	92.6
Total	68	100	68	100
p	< 0.001		< 0.001	

Comment: aCL-IgG (+) accounted for 20.6%, IgM (+) accounted for 7.4% with p <0.001.

Table 3.3. Average aCL concentration of acute cerebral infarction patients

aCL		*n*	$\overline{X}$	*SD*	*p*
IgG (GPL/mL)	Positive	14	33.98	29.42	< 0.01
	Negative	54	4.61	2.33	
	Total	68	10.66	7.76	
IgM (MPL/mL)	Positive	5	26.58	10.30	< 0.01
	Negative	63	2.68	2.27	
	Total	68	4.44	4.11	

Comment: aCL-IgG concentrations (+) was 33.98 ± 29.42 GPL/mL and average was 10.66 ± 7.76 GPL/mL; aCL-IgM levels (+) was 26.58 ± 10.30 MPL/mL and average was 4.44 ± 4.11 MPL/mL (p <0.01).

3.3. The correlation between aCL antibody with the risk factors and the severity of the disease

3.3.1. Correlation between aCL with risk factors

Table 3.4. Comparing the relationship between aCL with risk factors

Correlation	***aCL-IgG***		***aCL-IgM***	
	r	***p***	**r**	***p***
Glucose	-0.08	0.528	-0.07	0.546
Cholesterol	-0.14	0.274	-0.31	**0.011**
Triglycerid	-0.16	0.207	-0.07	0.596
HDL-C	-0.02	0.859	-0.084	0.494
LDL-C	-0.06	0.611	-0.25	**0.039**
Platelet	-0.109	0.375	0.234	0.054
Ure	-0.123	0.319	-0.119	0.332
Creatinin	-0.083	0.501	0.034	0.786
hs-CRP	-0.084	0.498	0.228	0.062
Fibrinogen	-0.040	0.743	0.234	0.054
HATT (mmHg)	-0.074	0.550	0.029	0.817
HATTr (mmHg)	-0.121	0.325	0.156	0.205
HATB (mmHg)	-0.109	0.378	0.102	0.410

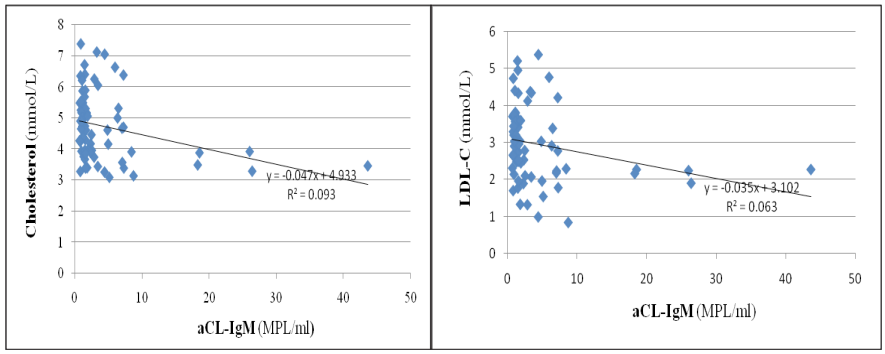


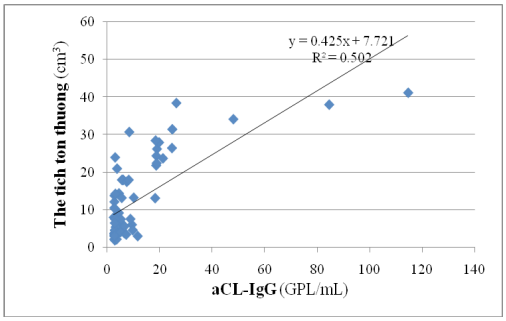
Figure 3.1. The correlation between the concentration of IgM aCL-cholesterol and LDL-C levels in acute cerebral infarction patients

Comment: aCL-IgM concentrations inversely correlated with the average level of cholesterol and LDL-C levels (r = -0.31; r = 0.25 and p < 0.05). No correlation between aCL-IgG with other risk factors with p > 0.05.

3.3.2. The correlation between aCL with the severity of patients

Table 3.5. The correlation between IgG-aCL with injury size and Glasgow scale

	aCL-IgG	
	r	***p***
The volume of brain damage	0.709	< 0.01
Glasgow scale at administration	-0.643	< 0.01



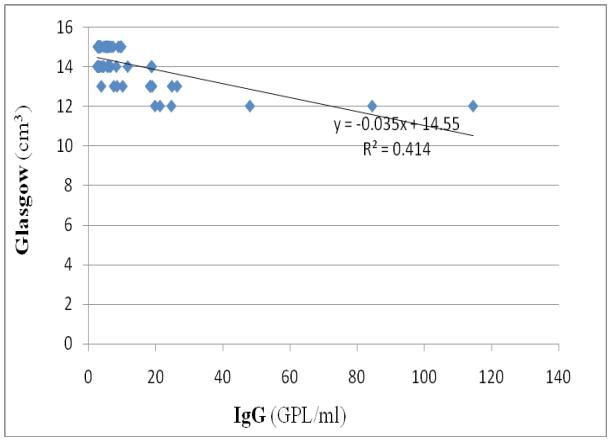
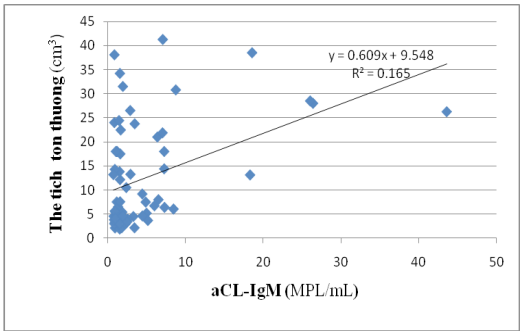


Chart 3.2. The correlation between IgM-aCL with injury size and glasgow scale

Close correlation between IgG aCL and volume of brain damage (r = 0.709; p < 0.01); and close inverse correlation with Glasgow score (r = -0.643; p < 0.01).

Table 3.6. The correlation between IgM-aCL with injury size and glasgow scale

correlation	*aCL-IgM*	
	r	***p***
The volume of brain damage	0.407	< 0.01
Glasgow scale at administration	-0.393	< 0.01



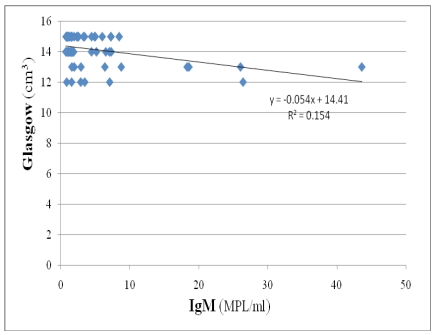


Chart 3.3. The correlation between IgM-aCL with injury size and glasgow scale

Moderate positive correlation between aCL-IgM with brain *injury size* (r = 0.407; p<0.05); and moderate inverse correlation with glasgow scale (r = -0.393; p < 0.01).

4. DISCUSSION

Through our study in 68 acute cerebral infarction patients, results showed that average age was 66.90 ± 12.16. In generally, acute cerebral infarction tended to increase with age between 50 and 80 years of age, and fell after 80. Our study also found that acute cerebral infarction dominately distributed in men, accounted for 58.8% than in females, 41.2%, proportion of male/female was no difference of 1.43 with p > 0.05. In the age groups, men still dominate except for the age group from 70 to 79, male and female were 50%. Results of the study was consistent with a number of other studies, such as:

Kitagawa Y studied on 250 acute cerebral infarction patients, aged 26-92 (mean 72 years), patients <50 years old, accounted for 5.2% and men accounted for 62%. Steven Levine R studied

on 132 acute cerebral infarction patients with positive aCL: aCL < 40 GPL group includes 111 patients with a mean age 63 ± 14 years old and the other group aCL > 40 GPL includes 21 patients, median age average of 54 ± 20 years. The study was also consistent with several studies in countries such as: Hoang Khanh, found that stroke increases with age and the proportion of men with cardiovascular disease was higher than women from 1.5 to 2 times, except ages from 35-44 and older than 85. Similar to other studies, Le Chuyen found the average age of patients was 72.64 ± 8.87 and acute cerebral infarction most dominant in group from 51 to 70 years old, male rate/female w 1.28. Ho Dien Tuong also found that the average age of 69.36 ± 12.22 years old in acute cerebral infarction patients, men dominate women, accounted for 57.58% and 42.42%, respectively; the proportion of male/female was 1.36.

4.1. Positive rate and average of aCL

In 68 acute cerebral infarction patients of our study, 14 patients with positive aCL-IgG, took 20.6% and average concentrations was 33.98 ± 29.42 GPL/mL, and the aCL-IgG percentage of male was higher than female (22.5% versus 17.9%); 5 patients with positive aCL-IgM at the rate of 7.4% and average concentrations was 26.58 ± 10.30 MPL/mL; the percentage of aCL-IgM was similar in male and female (7.5% compared to 7.1%). There was no difference in the rate of positive as well as the average aCL concentration between age groups and between sex ($p > 0.05$). Generally, positive rate of aCL in acute cerebral infarction patients in the studies on the world were in the range from 3 to 34.8%, the study also demonstrated that the aCL was the biological markers of the increased risk of cerebral infarction, especially in young women; Antiphospholipid syndrome is a disease characterized by suffering from venous arterial thrombosis and its presence is considered to be the cause of hypercoagulability lead to cerebral vascular accident, and be the most common of arterial thrombosis in the antiphospholipid syndrome, cerebral infarction.

Percentage of (+) aCL in our study is similar to the study published by several authors: Nagarajia D et al noted ratio of (+) aCL was 23%, aCL concentration was at average threshold of 21-60 MPL and of 21-100 GPL. Heizlef Olivier et al showed positive rate of aCL-IgG was 21% with the lowest concentration of 10 GPL, no cases of > 80 GPL. Husham YM Ali and colleagues showed that the (+) aCL rate of cerebral infarction patients was 22%.

Meanwhile, the rate of (+) aCL in our study was different than some other studies: according to a study of 524 cerebral infarction patients of Tubrim S et al, the proportion of patients with positive aCL was 34%, in which, 16% lower positive, 22.9 to 30 GPL or 10.9 to 15.0 MPL, 18% high positive, > 30.0 GPL or > 15.0 MPL. Another study of Hassab A. Ali and his colleagues recorded the proportion of (+) aCL 89 acute cerebral infarction, aged 20-65 years was 34.8%, the proportion of male/female was 1:1.6 and the presence of aPL as a risk of cerebral infarction. At the same time, our rate is higher than some authors such as research at the Academy of Neurology American noted 225 patients with first time cerebral infarction, (+) aCL rate was 9.7% and the presence of antibodies was an independent risk factor for cerebral infarction. The author Kitagawa Y at Tokai University Hachioji Hospital in Japan has recorded positive rate of aCL-IgG was 12%. In general, these all differences may be due to the limited sample size, the difference in the age group studied, as well as racial factors in our study and by selecting different cut-off threshold.

4.2. Correlation between aCL with risk factors

The researches on the world of aCL antibodies in cerebral infarction patients agree that aCL was considered a risk factor for disease, but some studies suggested that aCL antibody was an independent risk factor for cerebral infarction and studies also show that aCL related to stroke in the future but do not constitute an independent risk factor. To learn more about this problem we try to detect the relationship between aCL with other risk factors such as blood sugar, blood fat, protein inflammation as hs-CRP level phase, fibrinogen, kidney disease, the number of primary needs and condition of and hypertension of acute cerebral infarction patients.

In our study showed that aCL-IgG concentrations did not correlate with glucose and lipid profile parameters with $p > 0.05$; but aCL-IgM concentrations had negative correlation with average levels of total cholesterol and LDL-C with $p < 0.05$. No correlation between aCL IgG/IgM with urea, creatinine or platelet counts.

Similar to studies of L-Dumbrava Perju et al on 225 stroke patients showed no difference in the popularity of the risk factors for cerebral infarction and related diseases between (+) aCL and (-) aCL in patients with cerebral infarction. Retrospective study of Richard KT Chan and colleagues on 127 cases at the University Hospital of Wisconsin (USA) showed no differences for risk factors for cerebrovascular disease such as hypertension, diabetes, or hyperlipidemia. This study had the same result with our study, 1/14 cases having decreased platelet counts, proportion of 7.1%. A study of D.Nagaraja et al studied on 60 young cerebral infarction patients (≤ 40 years), they found that there was no difference between (+) aCL or (-) aCL for the risk factors such as diabetes, cholesterol, HDL-C and triglycerides. Ejaz Ahmed and colleagues found no difference in smoking status, age or sex. There was also no difference in the levels of blood cholesterol and HDL-C. Wolfgang MIESBACH and colleagues recorded 7% mild thrombocytopenia (median 108 G/L, the amount of 89-128 G/L), 42% hypertension, hypercholesterolemia 44%.

Overall the results of our study were similar to the those of majority of the studies in the world, only a few small details was similar to this study, but different to other studies. This is understandable due to differences in sample size, age group of objects, cut-off values of the tests as well as racial factors also make up a significant part of this difference.

4.3. The correlation between aCL and the severity of disease

The presence of aCL antibodies related to the severity of the disease in several studies of foreign authors. In this study we explored the relationship between aCL and the severity of the disease through the lesion volume and scale of Glasgow at administration of acute cerebral infarction patients, suggesting aCL-IgG levels had a close positive correlation with lesion volume of cerebral infarction with $r = 0.709$ and $p < 0.01$; and quite close inversely correlated with admission Glasgow Coma Scale with $r = - 0.643$ and $p < 0.01$. aCL-IgM levels have a positive correlation with moderate lesion volume with $r = 0.407$ and $p < 0.01$; and inverse correlation with Glasgow scale with $r = -0.393$ and $p < 0.01$. Positive correlation between aCL concentration and the damage severity of cerebral infarction as well as inverse correlation with the Glasgow scale showed that the higher levels of aCL the more severe of the disease. Like the study of Rosove MH et al on 70 acute cerebral infarction patients treated thrombosis showed recurrent thrombosis was a serious problem, and likely to happen for patients with circulating aCL antibodies. Research by Steven R Levine and colleagues studied 132 stroke patients with (+) aCL noted the embolism and mortality consequences after cerebral infarction associated with aCL-IgG may occur sooner and more frequently when the GPL > 40. Wolfgang et al MIESBACH retrospectively studied aPL test on 356 patients showed that the aCL in cerebral infarction can play an important role in the cause of various neurological syndromes.

In summary, the study showed that the aCL is biological marker of increased risk of cerebral infarction and related to the severity of the disease. However, our study had selected and exclused many other cerebral infarction cases as standard, so more research is needed, wider and deeper on this issue in the coming time.

5. CONCLUSION

There was an association between serum aCL antibodies (IgG, IgM) with some risk factors and severity in acute cerebral infarction patients. Serum aCL concentrations was high and correlated with the severity of cerebral infarction patient by lesion volume and scale of glasgow.

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