의학석사 학위논문

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2019년 8월

서울대학교 대학원

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# Abstract

# Effect of anti-phospholipid antibodies on the incidence of future cerebrovascular accident in patients with Moyamoya disease: A retrospective cohort study

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**Purpose:** To investigate the prevalence of antiphospholipid antibody (aPL) positivity and its clinical influence on the risk of cerebral diseases such as infarction or hemorrhage in patients with Moyamoya disease (MMD).

**Materials and methods:** A total of 515 patients with MMD who had visited SNUH between January 2011 and May 2016 and checked the level of aPL

(Anti-cardiolipin, anti-beta2-glycoprotein I and lupus anticoagulant) were included in this study. Proportion of patients with positive aPL antibodies in MMD was compared with that in 60 healthy controls. Clinical features at baseline and prevalence of cerebral events after baseline were analyzed according to the aPL positivity (aPL positive group vs. aPL negative group). Primary outcome in this study was the occurrence of cerebral hemorrhage or infarction (defined as the cerebrovascular event) in MMD patients during the follow-up, which was analyzed using Cox proportional hazard model. The mean (SD) follow-up period was 32.8 (47.5) months. There were no patients previously diagnosed as anti-phospholipid antibody syndrome or other autoimmune diseases.

**Results:** At baseline, 39 (7.6%) patients showed positive result in at least one antiphospholipid antibody or lupus anticoagulant tests, which was comparable to that in the healthy controls (5%). In the patients with MMD, baseline features such as age, gender, smoking status and other co-morbidities such as hypertension, dyslipidemia and diabetes were comparable between the aPL positive group and the aPL negative group.
During a total of 1914.5 person-year of observation, 63 cases of cerebral infarction occurred. In the univariate analysis, aPL positive group showed a significantly higher incidence of cerebral infarction (HR =2.30 95% CI =1.13 to 4.67). This result was consistent in the multivariable analysis where age,

gender, hypertension and dyslipidemia were adjusted (HR=2.06 95% CI =1.01 to 4.19). No specific clinical factors including aPL group significantly influence the cerebral hemorrhage risk in the univariable analysis.

**Conclusions:** The prevalence of aPL positivity was not different between the healthy control group and MMD patients group. However, positive aPL in MMD patients significantly increase the risk for future cerebral infarction.

**Key words:** moyamoya disease; moyamoya syndrome; stroke; cerebral infarction; antiphospholipid antibody

**Student number:** 2017-29212

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**MMD:** Moyamoya disease

**aPL**: antiphospholipid antibodies

**LA**: Lupus anticoagulant

**GPI**: glycoprotein I

**SNUH**: Seoul National University Hospital

**MRA**: Magnetic resonance angiography

**CBC**: complete blood count

**MMS**: Moyamoya syndrome

**APS**: antiphospholipid syndrome

**IRB**: institutional review board

**MRI**: Magnetic resonance image

**SD**: Standard deviation

**TIA**: transient ischemic attack

**IQR**: interquartile range

**SLE**: systemic lupus erythematosus

# Contents

# Introduction

Moyamoya disease (MMD) is characterized by progressive stenosis or occlusion of distal internal carotid arteries around the circle of Willis associated with abnormal, fine collateral vascular networks. (1, 2) It occurs in children and adults, showing a bimodal distribution of age at diagnosis. Clinical features between pediatric and adult-onset MMDs are quite different; most childhood-onset MMD patients shows cerebral ischemia whereas adult patients frequently present with intracranial hemorrhage. (3, 4) In addition, it had been believed that adult-onset MMD usually shows favorable prognosis without progression. However, recent population-based studies demonstrated that the incidence of ischemic attack in adult-onset MMD is much higher than recognized before. (5) This result suggests that revascularization surgery, which was mainly performed in pediatric MMD, could be beneficial in adult patients with high-risk for ischemic stroke. Therefore, defining risk factors which increase the risk for cerebral infarction is clinically important to determine appropriate treatment strategy in patients with adult-onset MMD.

Anti-phospholipid antibodies (aPL), which encompass lupus anticoagulant (LA), anti-cardiolipin antibodies and anti-beta2 glycoprotein I (anti-beta2 GPI), are a family of antibodies to phospholipid and phospholipid-

binding proteins. (6) These autoantibodies were proposed to induce prothrombotic state by interacting with many blood and vascular components such as monocyte, endothelial cell and platelet. (7-11) Many previous studies also suggested that presence of aPL was associated with increased risk for thrombosis in patients with various rheumatic diseases and even in the general population. (12-18) However, the relationship between aPL and MMD is still uncertain. There have been some case reports of ischemic stroke in patients with MMD and positive aPL but its prevalence and clinical relevance have not been investigated.

In the present study, we estimated the prevalence of positive aPL in a large, consecutive cohort of MMD patients in our institutions. In addition, we assessed the incidence of ischemic stroke in the study population to investigate whether the co-existence of positive aPL could impact the future stroke risk in patients with adult-onset MMD.

# Methods

### Study population

This study included patients who were diagnosed with MMD between January 2011 and May 2016 in Seoul National University Hospital (SNUH). All baseline and follow-up data were collected by reviewing the electronic medical database of the institution. Baseline date was defined as the day of visit at the SNUH due to clinical manifestation related to MMD. The diagnosis of MMD was based upon the characteristic cerebral angiographic pattern on magnetic resonance angiography (MRA), which was evaluated by two independent authors (EJH and KHK). At the baseline visit, complete blood tests such as complete blood count (CBC), coagulation tests, thyroid function test, ANA, ANCA and aPL were performed to exclude the secondary Moyamoya syndrome (MMS). Patients younger than 18 and those who have primary antiphospholipid syndrome (APS) or the conditions associated with MMS at baseline were excluded. No patients in this study took antiplatelet like aspirin. Included patients were classified into the two groups according to whether they showed at least one positive aPL (control group vs. aPL group). Proportion of patients with positive aPL in MMD was compared with that in 60 healthy controls.

The study was carried out in accordance with the Declaration of

Helsinki and was approved by the institutional review board (IRB). Consent was waived by the IRB due to the retrospective nature of the study.(1611-010-803)

**Detection of aPL**

All included patients who was clinically suspected as MMD had test for aPL. As described above, laboratory testing was performed when a patient is clinically stable without event of acute thrombosis or hemorrhage. Before May 2013, aPL tests included lupus anticoagulant and anti-cardiolipin assay. Test for anti-beta2GPI had been performed since May 2013.

For the lupus anticoagulant test, Peripheral blood was collected in commercially available sodium citrate tubes. After separation of platelet-free plasma, Lupus anticoagulant testing was performed using diluted Russell's viper venom assay. Detection of anti-cardiolipin and anti-beta2 GPI antibodies were performed according to the manufacturer's guideline by using the HemosIL AcuStar Antiphospholipid assay (Instrumentation Laboratory, Bedford, Massachusetts, USA). The results were considered positive when the titer of each antibody units exceeded 20 units.

**Follow-up and outcome assessment**

Included patients was followed up every 3 or 6 months. In each follow-up visit, complete history taking and neurologic examination were

performed by treating physicians to detect an ischemic or hemorrhagic event. If clinically suspected, brain magnetic resonance image (MRI) and MRA images were obtained to confirm the parenchymal alteration or vascular occlusion, respectively. The date of confirmation by image was defined as the one of outcome occurrence.

Each patient was followed up until either the date of cerebral infarction, hemorrhage, death or 1 June 2018, whichever came first. Primary outcome of the study was the ischemic stroke-free survival during the observation period between the two groups. Secondary outcomes included the incidence of intracranial hemorrhage during the observation period and the clinical factors which influence the risk for cerebral infarction.

**Statistical analysis**

All continuous values were presented as 'mean (standard deviation)'. Continuous and dichotomous variables between the two groups were compared using Student's t-test or Chi-square test, respectively. Incidence rate of outcome between the two groups were compared using Poisson regression. Cox proportional hazards regression model was used to estimate the effect of aPL positivity on the primary outcome. Incidence rate of ischemic stroke or intracranial hemorrhage were presented as the number of event per 100 person-years and compared using Poisson regression. All clinical factors clinically associated with the outcome were included in the univariable

analyses first. If it showed a relevant association ($p < 0.1$) in the univariable model, it was included in the multivariable model as a covariate.

All statistical analyses were performed using SPSS 25.0 software, and a P value <0.05 was considered statistically significant.

# Results

### Baseline characteristics of the included patients

Between January 2011 and May 2016, a total of 2200 patients were diagnosed with MMD in our institution and 515 of them were finally analyzed in this study (Figure 1). Briefly, mean (SD) age at baseline was 44.5 (13.4) years and 69.9% of the patients were female. Two-hundred ninety-eight (57.9%) patients had at least one history of transient ischemic attack (TIA) and it was the most common cause of the visit at baseline (n=298, 57.9%). Twenty-five (4.9%) and 48 (9.3%) of the patients had history of previous cerebral infarction and hemorrhage, respectively. At the baseline 75 (14.6%) patients visited our institution due to acute cerebral infarction or hemorrhage.

Among the included study population, 39 patients showed positive aPL test at baseline (aPL group). Anti-cardiolipin antibodies were most frequently positive (33/39, 84.6%) and five patients showed positive result in more than 1 of anti-phospholipid antibodies. Baseline clinical features of the included patients were presented in Table 1. Proportions of smokers and those who had risk factors (hypertension, diabetes and dyslipidemia) for cerebrovascular disease were not significantly different between the two groups. The proportion of patients with previous history of CVA was also comparable.

### Incidence of cerebral infarction or hemorrhage during the observation

**period**

During a total of 1914.5 person-years of the observation, 63 cases of cerebral infarction occurred, with an incidence rate of 3.3 (95% CI 2.5 to 4.2) per 100 person-years. Median (IQR) time between the baseline and cerebral infarction was 794 (971) days and 35 cases (55.6%) occurred within 1 year from the baseline. Baseline characteristics of the patients with cerebral infarction was presented in table 4. There were 46 cases of intracranial hemorrhage during the observation, with an incidence rate of 2.4 (1.5 to 2.7) per 100 person-years. Median (IQR) time to cerebral hemorrhage was 1002 (856) days.

In the 63 cases of cerebral infarction, 9(23.1%) patients were in the aPL group. Incidence rate of cerebral infarction in the aPL group was significantly higher than that in the control group (Incidence rate ratio = 2.46, 95% CI 1.22 to 4.98) (Figure 2). In contrast, there was no difference regarding the incidence of cerebral hemorrhage between the two groups (Figure 3).

**Risk factors for cerebral infarction and hemorrhage**

Univariable Cox analyses showed that older age was significantly associated with the increased risk for future cerebral infarction (Table 2). In contrast, previous history of cerebral hemorrhage before baseline was associated with lower risk for future cerebral infarction. Hypertension,

gender, smoking status and dyslipidemia were not associated with the outcome. Interestingly, the aPL group was most important factor which increased the risk for future infarction in the study population (HR =2.30 95% CI =1.13 to 4.67). This result was consistent with multivariable analysis in which other clinically relevant variables were included (adjusted HR=2.06 95% CI =1.01 to 4.19).

According to the cerebral hemorrhage, no specific clinical factors including aPL group significantly influence the cerebral hemorrhage risk in the univariable analysis (Table 3).

**Sensitivity analysis**

Since, it is possible that acute thrombotic event at baseline could influence the result of aPL assays, we performed the same cox regression analysis after excluding 75 patients who had an acute cerebral infarction within 30 days before the baseline. However, the influence of aPL group on the occurrence of future cerebral infarction was unaffected (adjusted HR 2.15, 95% CI 1.00 to 4.62) (Table 5).

In addition, we thought the bypass surgery could affect the risk of cerebral infarction. So we repeated the cox regression after including history of bypass surgery in observational period. Finally, the bypass surgery significantly reduced the infarction rate (HR 0.46, 95% CI 0.28 to 0.78 p=0.004). There was no difference in the protective effect of bypass surgery

on the cerebral infarction, whether aPL antibody positive or not. (Table 6)

# Discussion

According to the literature, aPL positivity is observed in the 1~5% of the general population. (19) Previous studies of aPL in MMD were only case reports. (12, 20-23) which did not reflect on the association of aPL with MMD nor even identify the prevalence of aPL in MMD. In this study, we describe the prevalence of aPL positivity in MMD and evaluated the relationships between the presence of aPL and clinical outcomes in MMD. The prevalence of aPL positivity in our study were 5% in healthy control group and 7.6% in MMD patient group. There was no significant aPL positivity difference between the two groups.

It has been reported that presence of aPL generally increases the risk for cerebrovascular diseases. (24) Some investigators have postulated that APS with MMD is the MMS such as systemic lupus erythematosus (SLE), Down's syndrome, Marfan syndrome, sickle cell anemia, auto immune thyroiditis, or some of cerebral infections. (12, 25) In this study, we excluded patients with primary APS or the conditions associated with MMS at baseline. This study was conducted to investigate how aPL positivity affects MMD patients with idiopathic distal ICA stenosis, as it relates to its effect on the clinical outcome including cerebrovascular accident occurrence. In the present study, Patients with three or more atherosclerosis risk factors

(dyslipidemia, heavy smoking, alcoholics and hypertension) were excluded from the diagnosis of the MMD, as was used in other literature, to identify only pure MMD patients. (26, 27)

Overall annual stroke rate was 5.7%; 3.3% for ischemic stroke and 2.4% for hemorrhage stroke. The rates of cerebral infarction and hemorrhage in aPL positive MMD of this study were 23.1% and 5.1%, respectively. The rates of cerebral infarction and hemorrhage in aPL negative MMD of this study were 11.4% and 9.3%, respectively. The overall stroke rates seen in our study were in accordance with the previous reports. (5, 28) However the rate of cerebral infarction in aPL positive MMD patients was higher than that in aPL negative MMD patients. Five patients were dual aPL positive in this study. Two out of five showed cerebral infarction, one showed cerebral hemorrhage during the observational period. The more stroke occurred in dual aPL positive patients. Although the number of patients was too small to be statistically significant. This result consistent with the fact that in the literature, dual aPL positivity had more thrombosis. (29)

The aPL is strongly associated with arterial and venous thrombosis produced by immune system. (30) Concept of aPL in thrombosis has been well known for over 30years but, its thrombogenic pathophysiology is still unclear. (31) It has not been clearly identified whether the aPL positivity is due to the distal ICA stenosis of the MMD or the generation of the distal ICA stenosis is caused by aPL. The interaction of aPL with endothelial cell has

been suggested as a probable mechanism for thrombosis. In MMD patients endothelial cell alterations may be a source of autoantigens that play a role in making the secondary APS that reacts to the exposed phospholipid components of the endothelial cell membrane. (32) On the other hand Booth et al. have assumed that the development of the blood vessel pattern of APS into a moyamoya type of vascular pattern could be secondary to initial thrombosis and stenosis of the basal cerebrovascular system. (12) In our study, the prevalence of aPL in MMD patients was not meaningfully higher than that in the healthy control group, and the imaging characteristics of aPL positive MMD patients did not differ from those of aPL negative MMD patients. Therefore, it is difficult to explain the which of the occurrence of MMD and presence of aPL precedes the other. However, as our research showed, cerebral infarction occurred more frequently in aPL positive MMD patients. It can be posited that positive aPL can increase the risk of future cerebral infarction in MMD patients. This predictive effect was more prominent in the subgroup of patients who did not show a significant cerebral hemorrhage or infarction at initial presentation. This could be interpreted in the same context as the previous study where patients with aPL had significantly increased risk of arterial and venous thrombosis. (6) aPL positivity can exacerbate the risk of cerebral infarction in MMD patients who already have higher infarction risk compared to the healthy patients due to distal ICA stenosis. Cho at al. had previously reported that patients with

cerebral hemorrhage and infarction in MMD tend to develop recurrent cerebral hemorrhage and infarction, respectively. (33) In this study, similar to the previous paper, there was a tendency to develop less infarction in a group with previous hemorrhagic stroke events. In our study, positive aPL in MMD did not influence the incidence of cerebral hemorrhage. Kerenyi et al. insist that positive aPL patients had increased risk of hemorrhage despite their young age. (34) As you can see from the data, bypass surgery was effective in preventing cerebral infarction in MMD patients, although it was not related to aPL.

This study has some limitations. First, our data are based on reviewing the electronic medical database of one institution retrospectively. Second, there are small number of MMD patients with aPL positive. Therefore, we cannot analyze the statistics in more detail. Only 13 patients with positive aPL performed repetitive laboratory evaluation. Therefore, there is a possibility that true APS will be diagnosed.

Even though this study is a retrospective study, it showed that MMD patients with positive aPL can anticipate the increased risk of cerebral infarction. Therefore, when diagnosing MMD, it is necessary to pay more attention to antiplatelet or anticoagulation for aPL positive patients. Further study is needed to analyze the implementation of more aggressive treatment methods that may reduce future cerebral infarction.

# CONCLUSIONS

The prevalence of aPL positivity was not different between the healthy control group and MMD patients group. However, positive aPL in MMD patients significantly increase the risk for future cerebral infarction.

**Figure.1** Study participant selection.

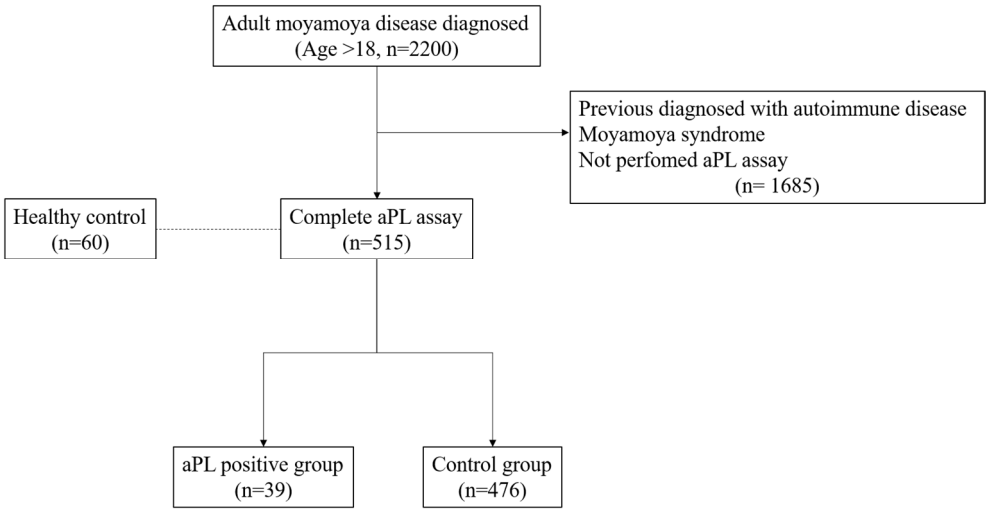
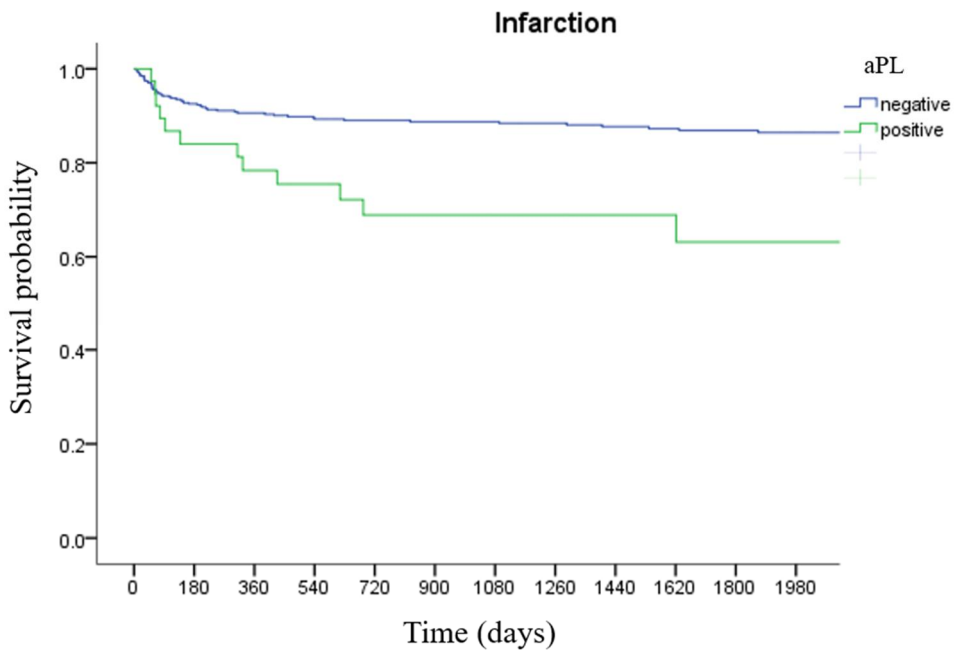
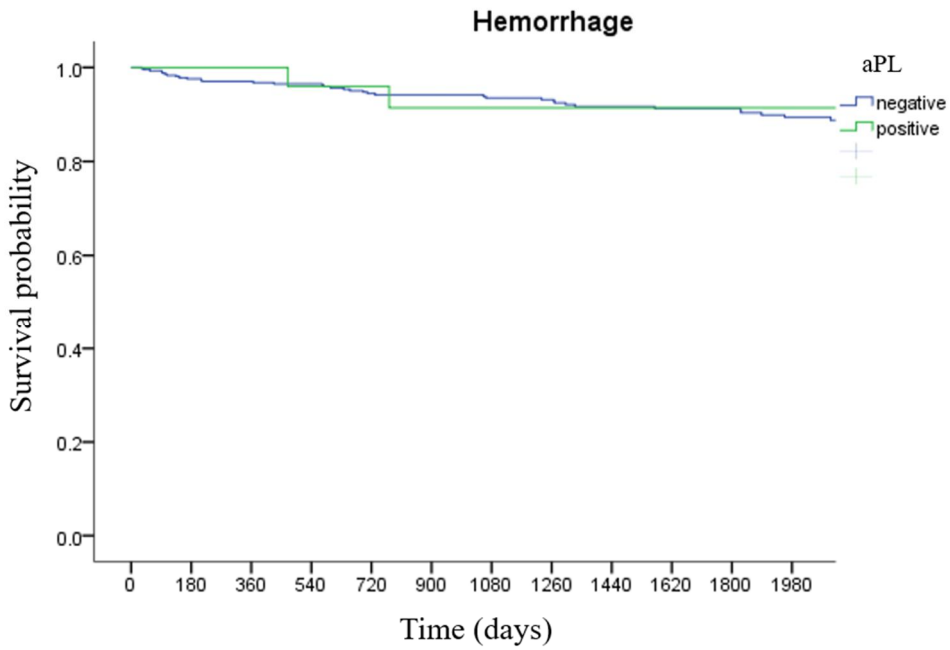


**Figure. 2** The Kaplan-Meier curve for the cerebral infarction.




There is a significant difference in infarction, depending on aPL positivity.

**Figure. 3** Kaplan-Meier curve for the cerebral hemorrhage.




The curve showing a statistically no difference in hemorrhage, depending on whether aPL is positive or not.

**Table 1.** Baseline characteristics of patients

| | aPL neg (N=476) | aPL pos (N=39) | P value |
|---|---|---|---|
| Age, year, mean (SD) | 44.5 (13.2) | 44.8 (15.2) | 0.897 |
| Male sex, n (%) | 140 (29.4) | 15 (38.5) | 0.236 |
| Familial MMD, n (%) | 46 (9.7) | 1 (2.6) | 0.139 |
| Current smoker, n (%) | 70 (14.9) | 8 (20.5) | 0.349 |
| Hypertension, n (%) | 183 (38.9) | 17 (43.6) | 0.560 |
| Diabetes mellitus, n (%) | 49 (10.4) | 5 (12.8) | 0.637 |
| Dyslipidemia, n (%) | 159 (33.9) | 15 (38.5) | 0.564 |
| Previous Hx of TIA, n (%) | 277 (58.6) | 21 (56.8) | 0.679 |
| Previous Hx of significant cerebral infarction, n (%) | 21 (4.4) | 4 (10.3) | 0.103 |
| Previous Hx of significant cerebral hemorrhage, n (%) | 44 (9.3) | 4 (10.5) | 0.794 |
| Previously asymptomatic, n (%) | 27 (5.7) | 3 (7.7) | 0.605 |
| FANA positive, n (%) | 9 (1.9) | 2 (5.1) | 0.201 |
| Rheumatoid factor positive, n (%) | 28 (5.9) | 1 (2.6) | 0.714 |
| Cryoglobulin positive, n (%) | 7 (1.5) | 0 (0.0) | 0.452 |
| Low protein C, n (%) | 12 (2.6) | 2 (5.3) | 0.293 |
| Low protein S, n (%) | 123 (25.8) | 7 (17.9) | 0.275 |
| Low anti-thrombin, n (%) | 23 (5.1) | 1 (2.7) | 1.000 |

aPL: antiphospholipid antibody, neg: negative, pos: positive, MMD: moyamoya disease, Hx: history, TIA: transient ischemic attack, FANA: fluorescent antinuclear antibody

**Table 2.** Univariable and multivariable Cox analyses for cerebral infarction

| Clinical features | Univariable analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | P | HR | 95% CI | P |
| Age | 1.03 | 1.01 to 1.05 | 0.009 | 1.03 | 1.01 to 1.05 | 0.008 |
| Male sex | 1.05 | 0.61 to 1.79 | 0.872 | * | | |
| Familial type | 0.65 | 0.24 to 1.79 | 0.650 | * | | |
| Smoking Hx | 0.75 | 0.36 to 1.59 | 0.455 | * | | |
| Previous infarction | 1.12 | 0.51 to 2.48 | 0.777 | * | | |
| Previous hemorrhage | 0.23 | 0.06 to 0.94 | 0.040 | 0.23 | 0.05 to 0.93 | 0.039 |
| HTN | 0.89 | 0.53 to 1.48 | 0.650 | * | | |
| DM | 1.29 | 0.64 to 2.63 | 0.479 | * | | |
| Dyslipidemia | 0.97 | 0.58 to 1.63 | 0.910 | * | | |
| aPL positive | 2.30 | 1.13 to 4.67 | 0.022 | 2.06 | 1.01 to 4.19 | 0.047 |

*, was not included in the multivariable model due to lack of relevance in the univariable analysis. aPL: antiphospholipid antibody

**Table 3.** Univariable and multivariable Cox analyses for cerebral hemorrhage

| Clinical features | Univariable analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | P | HR | 95% CI | P |
| Age | 1.02 | 0.99 to 1.05 | 0.238 | | | |
| Male sex | 1.14 | 0.52 to 2.50 | 0.751 | | | |
| Familial type | 1.05 | 0.32 to 3.46 | 0.942 | | | |
| Smoking Hx | 0.38 | 0.09 to 1.59 | 0.184 | | | |
| Previous infarction | 0.04 | 0.00 to 7.81 | 0.233 | | | |
| Previous hemorrhage | 0.78 | 0.23 to 2.59 | 0.678 | | | |
| HTN | 0.96 | 0.46 to 2.02 | 0.915 | | | |
| DM | 1.71 | 0.65 to 4.53 | 0.278 | | | |
| Dyslipidemia | 0.93 | 0.44 to 1.98 | 0.847 | | | |
| aPL positive | 1.11 | 0.26 to 4.66 | 0.892 | | | |

aPL: antiphospholipid antibody

**Table 4.** Baseline characteristics of the patients with cerebral infarction

| Variable | N=63 |
|---|---|
| Age, year, mean (SD) | 50 (14.1) |
| Male sex, n (%) | 23 (36.5) |
| Familial MMD, n (%) | 3 (4.76) |
| Current smoker, n (%) | 11 (17.5) |
| Hypertension, n (%) | 30 (47.6) |
| Diabetes mellitus, n (%) | 13 (20.6) |
| Dyslipidemia, n (%) | 25 (39.7) |
| Previous Hx of TIA, n (%) | 42 (66.7) |

MMD: moyamoya disease, Hx: history, TIA: transient ischemic attack

**Table 5.** Sensitivity analysis. After excluding 75 patients who had an acute cerebral infarction within 30 days.

| | Univariable analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|
| Clinical features | HR | 95% CI | P | HR | 95% CI | P |
| Age | 1.03 | 1.01 to 1.05 | 0.003 | 1.03 | 1.01 to 1.05 | 0.003 |
| Male sex | 1.16 | 0.65 to 2.05 | 0.618 | * | | |
| Familial type | 0.55 | 0.17 to 1.75 | 0.309 | * | | |
| Smoking Hx | 0.81 | 0.37 to 1.80 | 0.603 | * | | |
| Previous infarction | 1.42 | 0.63 to 3.15 | 0.398 | * | | |
| Previous hemorrhage | 0.27 | 0.06 to 1.11 | 0.070 | 0.26 | 0.06 to 1.07 | 0.061 |
| HTN | 1.01 | 0.59 to 1.74 | 0.973 | * | | |
| DM | 1.38 | 0.65 to 2.92 | 0.406 | * | | |
| Dyslipidemia | 0.97 | 0.56 to 1.69 | 0.908 | * | | |
| aPL positive | 2.55 | 1.20 to 5.41 | 0.015 | 2.15 | 1.00 to 4.62 | 0.049 |

*, was not included in the multivariable model due to lack of relevance in the univariable analysis. Hx: history, aPL: antiphospholipid antibody

**Table 6.** Sensitivity analysis. Multivariable analysis for cerebral infarction after including bypass surgery

| | Multivariable analysis | | |
|---|---|---|---|
| Clinical features | HR | 95% CI | P |
| Age | 1.02 | 1.00 to 1.04 | 0.039 |
| Previous hemorrhage | 0.22 | 0.06 to 1.07 | 0.035 |
| aPL positive | 2.21 | 1.00 to 4.61 | 0.030 |
| Bypass surgery | 0.46 | 0.28 to 0.78 | 0.004 |

aPL: antiphospholipid antibody

# References


1. Natori Y, Ikezaki K, Matsushima T, Fukui M. 'Angiographic moyamoya' its definition, classification, and therapy. Clin Neurol Neurosurg. 1997;99 Suppl 2:S168-72.
2. Suzuki J, Takaku A. Cerebrovascular "moyamoya" disease. Disease showing abnormal net-like vessels in base of brain. Arch Neurol. 1969;20(3):288-99.
3. Ikezaki K, Han DH, Kawano T, Kinukawa N, Fukui M. A clinical comparison of definite moyamoya disease between South Korea and Japan. Stroke. 1997;28(12):2513-7.
4. Kim JS. Moyamoya disease: epidemiology, clinical features, and diagnosis. J stroke. 2016;18(1):2.
5. Kim T, Lee H, Bang JS, Kwon O-K, Hwang G, Oh CW. Epidemiology of moyamoya disease in Korea: based on national health insurance service data. J Korean Neurosurg Soc. 2015;57(6):390.
6. Willis R, Pierangeli SS. Pathophysiology of the antiphospholipid antibody syndrome. Auto Immun Highlights. 2011;2(2):35-52.
7. Chen PP, Giles I. Antibodies to serine proteases in the antiphospholipid syndrome. Curr Rheumatol Rep. 2010;12(1):45-52.
8. Krone KA, Allen KL, McCrae KR. Impaired fibrinolysis in the antiphospholipid syndrome. Curr Rheumatol Rep. 2010;12(1):53-7.
9. Meroni P, Raschi E, Camera M, Testoni C, Nicoletti F, Tincani A, et al. Endothelial activation by aPL: a potential pathogenetic mechanism for the clinical manifestations of the syndrome. J Autoimmun. 2000;15(2):237-40.
10. Nojima J, Suehisa E, Kuratsune H, Machii T, Koike T, Kitani T, et al. Platelet activation induced by combined effects of anticardiolipin and lupus anticoagulant IgG antibodies in patients with systemic lupus erythematosus. Thromb Haemost. 1999;81(03):436-41.

11. Urbanus R, Derksen R, de Groot P. Platelets and the antiphospholipid syndrome. Lupus. 2008;17(10):888-94.
12. Booth F, Yanofsky R, Ross IB, Lawrence P, Oen K. Primary antiphospholipid syndrome with moyamoya-like vascular changes. Pediatr Neurosurg. 1999;31(1):45-8.
13. Corban MT, Duarte-Garcia A, McBane RD, Matteson EL, Lerman LO, Lerman A. Antiphospholipid syndrome: role of vascular endothelial cells and implications for risk stratification and targeted therapeutics. J Am Coll Cardiol. 2017;69(18):2317-30.
14. Farmer-Boatwright MK, Roubey RA. Venous thrombosis in the antiphospholipid syndrome. Arterioscler Thromb Vasc biol. 2009;29(3):321-5.
15. Garcia D, Akl EA, Carr R, Kearon C. Antiphospholipid antibodies and the risk of recurrence after a first episode of venous thromboembolism: a systematic review. Blood. 2013;122(5):817-24.
16. Moroni G, Ventura D, Riva P, Panzeri P, Quaglini S, Banfi G, et al. Antiphospholipid antibodies are associated with an increased risk for chronic renal insufficiency in patients with lupus nephritis. Am J Kidney Dis. 2004;43(1):28-36.
17. Ortel TL. Thrombosis and the antiphospholipid syndrome. Hematology Am Soc Hematol Educ Program Book. 2005;2005(1):462-8.
18. Tektonidou MG, Laskari K, Panagiotakos DB, Moutsopoulos HM. Risk factors for thrombosis and primary thrombosis prevention in patients with systemic lupus erythematosus with or without antiphospholipid antibodies. Arthritis Rheum. 2009;61(1):29-36.
19. Petri M. Epidemiology of the antiphospholipid antibody syndrome. J Autoimmun. 2000;15(2):145-51.
20. Bakdash T, Cohen AR, Hempel JM, Hoagland J, Newman AJ.

Moyamoya, dystonia during hyperventilation, and antiphospholipid antibodies. Pediatr Neurol. 2002;26(2):157-60.

21. Carhuapoma JR, D'Olhaberriague L, Levine SR. Moyamoya syndrome associated with Sneddon's syndrome and antiphospholipid-protein antibodies. J Stroke Cerebrovasc Dis. 1999;8(2):51-6.

22. Shuja-Ud-Din MA, Ahamed SA, Baidas G, Naeem M. Moyamoya syndrome with primary antiphospholipid syndrome. Med Princ Pract. 2006;15(3):238-41.

23. Wang Z, Fu Z, Wang J, Cui H, Zhang Z, Zhang B. Moyamoya syndrome with antiphospholipid antibodies: a case report and literature review. Lupus. 2014;23(11):1204-6.

24. Alarcon-Segovia D. Clinical manifestations of the antiphospholipid syndrome. J Rheumatol. 1992;19(11):1778-81.

25. Yamada H, Deguchi K, Tanigawara T, Takenaka K, Nishimura Y, Shinoda J, et al. The relationship between moyamoya disease and bacterial infection. Clin Neurol Neurosurg. 1997;99:S221-S4.

26. Jeon JP, Kim JE. A recent update of clinical and research topics concerning adult moyamoya disease. J Korean Neurosurg Soc. 2016;59(6):537.

27. Kim JE, Jeon JS. An update on the diagnosis and treatment of adult Moyamoya disease taking into consideration controversial issues. Neurol Res. 2014;36(5):407-16.

28. Cho W-S, Chung YS, Kim JE, Jeon JP, Son YJ, Bang JS, et al. The natural clinical course of hemodynamically stable adult moyamoya disease. J Neurosurg. 2015;122(1):82-9.

29. Lee EY, Lee CK, Lee TH, Chung SM, Kim SH, Yoo B, et al. Does the anti beta2 glycoprotein I antibody provide additional information in patients with thrombosis? Thromb Res. 2003;111(1-2):29-32

30. Hughes GR. The antiphospholipid syndrome: ten years on. Lancet.

1993;342(8867):341-4.
31. Islam MA, Alam F, Sasongko TH, Gan SH. Antiphospholipid Antibody-Mediated Thrombotic Mechanisms in Antiphospholipid Syndrome: Towards Pathophysiology-Based Treatment. Curr Pharm Des. 2016;22(28):4451-69.
32. Bonduel M, Hepner M, Sciuccati G, Torres AF, Tenembaum S. Prothrombotic disorders in children with moyamoya syndrome. Stroke. 2001;32(8):1786-92.
33. Cho WS, Chung YS, Kim JE, Jeon JP, Son YJ, Bang JS, et al. The natural clinical course of hemodynamically stable adult moyamoya disease. J Neurosurg. 2015;122(1):82-9.
34. Kerenyi L, Kardos L, Szasz J, Szatmári S, Bereczki D, Hegedüs K, et al. Factors influencing hemorrhagic transformation in ischemic stroke: a clinicopathological comparison. Eur J Neurol. 2006;13(11):1251-5.

# 국 문 초 록

**목적:** 모야모야병 환자에서 항인지질 항체 양성률을 조사하고, 항인지질 항체 검사 양성여부가 뇌경색이나 뇌출혈과 같은 뇌졸중의 발생에 미치는 임상적 영향을 알아보고자 한다.

**방법:** 2011 년 1 월부터 2016 년 5 월까지 서울대병원에서 모야모야병을 진단 받은 2200 명의 환자 중에 515 명의 환자를 대상으로 항인지질 항체(항카디오리핀항체, 항베타 2-당단백 1 항체, 루푸스항응고인자) 검사를 시행하였다. 모야모야병 환자의 항인지질 항체 양성률을 비교하기 위해 60 명의 건강한 정상대조군과 비교하였다. 그리고 항인지질항체 양성인 환자군과, 항인지질항체 음성인 환자군의 임상적 특성을 분석하였다. 본 연구의 주된 결과는 연구기간 중 모야모야환자에서 뇌출혈이나 뇌경색이 발생하는 것으로 정의 하였고 그것을 Cox 의 비례위험모형을 이용하여 위험인자를 분석하는 연구를 진행하였다. 모든 환자는 이전에 항인지질항체 증후군이나 다른 자가면역질환을 진단 받은 적이 없었고, 평균 추적관찰기간은 32.8 개월(표준편차 47.5)이었다.

**결과:** 모야모야병 환자에서 적어도 하나의 항인지질항체의 양성은 39 명(7.6%)의 환자에서 관찰되었고, 이는 건강대조군(5%)에서의 항인지질 항체 양성률과 거의 차이가 없었다. 모야모야병 환자의 기본적인 임상적 특성에서 항인지질항체 양성군과 음성군 사이에 나이, 성별, 흡연여부, 이외에 고혈압, 고지혈증, 당뇨와 같은 동반질환의 유뮤는 각 그룹간에 차이는 없었다. 총 1914.5 인년의 관찰기간동안, 63 건의 뇌졸중이 일어났고, 단변량분석을 하였을 때, 항인지질항체 양성군에서 뇌졸중이 더 많은 빈도로

발생한 것을 알 수 있었다. (HR =2.30 95% CI =1.13 to 4.67)이 결과는 나이, 성별, 고혈압, 고지혈증등을 교정한 다변량 분석에서도 같은 결과를 보였다. (HR=2.06 95% CI =1.01 to 4.19) 관찰기간 동안 뇌출혈의 발생은 항인지질 항체 양성 여부와는 관련이 없었다.

**결론:** 모야모야 환자에서 항인지질항체 검사 양성을 보이는 경우 추후 뇌경색을 일으킬 가능성이 높다.

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**주요어:** 모야모야병, 모야모야증후군, 뇌졸중, 뇌경색, 항인지질 항체

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