



HAL
open science

Moyamoya Angiopathy and Antiphospholipid Antibodies: A Coincidental Association?

Lina Grosset, Alain Stepanian, Marc-Antoine Labeyrie, Vittorio Civelli,
Hugues Chabriat, Virginie Siguret, Dominique Hervé

► **To cite this version:**

Lina Grosset, Alain Stepanian, Marc-Antoine Labeyrie, Vittorio Civelli, Hugues Chabriat, et al.. Moyamoya Angiopathy and Antiphospholipid Antibodies: A Coincidental Association?. Stroke, 2024, Online ahead of print. 10.1161/STROKEAHA.124.048852 . hal-04828694

HAL Id: hal-04828694

<https://hal.science/hal-04828694v1>

Submitted on 10 Dec 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Moyamoya Angiopathy and Antiphospholipid Antibodies: A Coincidental Association?

Lina Grosset ¹, Alain Stepanian ², Marc-Antoine Labeyrie ³, Vittorio Civelli ³, Hugues Chabriat ¹, Virginie Siguret ⁴, Dominique Hervé ¹

¹ APHP-Hôpital Lariboisière-CERVCO, INSERM-U1141, FHU-NeuroVasc-Université Paris-Cité, France (L.G., H.C., D.H.).

² CHU de Montpellier, Université de Montpellier, PhyMedExp Inserm CNRS, France (A.S.).

³ APHP-Nord-Hôpital Lariboisière, Neuroradiologie interventionnelle, INSERM-U942, Paris, France (M.-A.L., V.C.).

⁴ APHP-Nord-Hôpital Lariboisière, Hématologie Biologique, INSERM-U1140, Paris, France (V.S.).

Keywords:

antibodies, antiphospholipid; lupus coagulation inhibitor; prevalence; stroke.

Correspondence to:

Dominique Hervé, MD, Hôpital Lariboisière, 2 rue Ambroise Paré, 75010, Paris, France.

Email

dominique.herve@aphp.fr

Abstract

Background:

The presence of antiphospholipid antibodies (aPL) has been suggested as a potential cause of moyamoya angiopathy (MMA), but this remains uncertain. In this case-control study, we aimed to compare the prevalence of circulating aPL in patients with MMA and in non-MMA cerebrovascular controls.

Methods:

For comparison, we included 95 patients with MMA from the French National Referral Centre for this condition and 182 age- and sex-matched non-MMA controls with a different cerebrovascular disease, all younger than 55 years. Anticardiolipin antibodies, anti- β 2-glycoprotein I antibodies, and lupus anticoagulant were assessed using the guidelines of the International Society on Thrombosis and Haemostasis.

Results:

aPL prevalence was 22% in patients with MMA and 25% in controls ($P=0.74$) with no differences in aPL subtypes between the 2 groups. The prevalence of transient ischemic attacks, ischemic stroke, and hemorrhagic stroke did not differ between patients with aPL-positive and aPL-negative MMA.

Conclusions:

The prevalence of aPL in patients with MMA is comparable to that in non-MMA controls. The present results do not support any causal relationship between aPL and MMA.

Nonstandard Abbreviations and Acronyms

aPL	antiphospholipid antibody
APS	antiphospholipid syndrome
aβ2GPI	anti- β 2-glycoprotein I
MMA	moyamoya angiopathy
MMS	moyamoya syndrome
TIA	transient ischemic attack

Moyamoya angiopathy (MMA) is characterized by progressive stenosis of the supraclinoid internal carotid arteries and abnormal basal collateral vessel development. MMA is classified as moyamoya disease when idiopathic and moyamoya syndrome (MMS) when associated with inherited multisystemic disorders or acquired conditions.¹ Conventional antiphospholipid antibodies (aPL) consist of anticardiolipin antibodies, a β 2GPI (anti- β 2-glycoprotein I antibodies), and lupus anticoagulant.² Several cases of coexistence of aPL and MMS have been reported over the past years, suggesting potential pathogenic relationships.^{3–7} A possible involvement of aPL in the alterations of endothelial or subendothelial structures has even been suggested.⁶ However, whether this association is causal or coincidental remains unknown. Thus, we aimed to compare the prevalence of blood-circulating aPL in patients with MMA and in patients with a non-MMA cerebrovascular disease.

METHODS

This study follows the Strengthening the Reporting of Observational Studies in Epidemiology guidelines. The data that support the findings of this study are available from the corresponding author upon reasonable request. Missing data were considered for analysis. Informed consent was obtained from participants, and the protocol study was approved by an independent ethics evaluation committee. Patients with MMA diagnosed according to the most current definition and confirmed by both a vascular neurologist (D.H.) and a neuroradiologist (M.-A.L./V.C.) were recruited from the moyamoya cohort of the French National Referral Centre (www.cervco.fr) at the Lariboisiere Hospital between January 2010 and December 2022.¹ Details of this cohort have been reported and are summarized in Supplemental Material.⁸ The control group included consecutive patients without MMA admitted to the same hospital stroke care unit during the same period. Controls were matched 2:1 for sex, age, and aPL assay. Only patients and controls under 55 years were included, as aPL assays were not systematically performed on controls older than 55 years admitted to the stroke care unit.

Table 1. Demographic, Ethnicity, and aPL Profile Characteristics

	MMA, n=95	Control, n=182	P value
Sex, women	64 (67%)	126 (69%)	0.71
Age at test, y; median (IQR)	37 (28–43)	36 (28–42)	0.50
Ethnicity			
European	61 (64)	126 (69)	0.06
African	18 (19)	41 (23)	
East Asian	13 (14)	8 (4)	
Other	3 (3)	7 (4)	
aPL profile			
Any aPL-positive test*	21 (22%)	45 (25%)	0.74
aCL (IgG or IgM) positivity*	19 (20%)	35 (19%)	1
IgG	14 (15%)	23 (13%)	0.76
IgM	6 (6%)	15 (8%)	0.74
aβ2GPI IgG positivity*	1 (1%)	8 (4%)	0.26
Lupus anticoagulant	1/45 (2%)	8/102 (8%)	0.27
Triple positive†	0	2 (1%)	

Moderate-to-high titers positivity in MMA/controls: aCL: n=3/6; aβ2GPI: n=0/3. aCL indicates anticardiolipin antibodies; aPL, antiphospholipid antibody; aβ2GPI, anti-β2-glycoprotein I; IQR, interquartile range; and MMA, moyamoya angiopathy.

*Manufacturer's positivity threshold.

†Triple positive profile defined as the presence of aCL, aβ2GPI, and lupus anticoagulant.

IgG/IgM anticardiolipin antibodies and IgG aβ2GPI were titrated using solid-phase immunoassays (Table S1). We pre-specified 2 cutoff values: the manufacturer's positivity threshold corresponding to the 99th percentile of healthy volunteers for each assay with patients classified as positive or negative; a second threshold for moderate-to-high antibody titers, namely >40 units for Enzyme-Linked-Immuno-Sorbent-Assay/Fluorescence-Labeled-Enzyme-Immuno-Assay and >200 units for Chemi-Luminescent-Immuno-Assay according to the 2023 propositions of the American College of Rheumatology and the European Alliance of Associations for Rheumatology.² Lupus anticoagulant diagnosis was made in plasma, only after 2015, using current recommendations.⁹ Comparisons between groups were made using

Wilcoxon rank-sum tests for continuous variables and χ^2 tests for categorical data.

RESULTS

We included 95 patients with MMA, predominantly female (67%) and of European origin (64%), with a median age of 37 years (Table 1). Among them, 36% had MMS with associated conditions, including neurofibromatosis type 1, Down syndrome, other rare genetic forms of MMS, cranial irradiation, or autoimmune diseases. Cerebrovascular manifestations in this group consisted of transient ischemic attack (TIA), ischemic stroke, and hemorrhagic stroke in 47% (n=45), 48% (n=46), and 19% (n=18) of cases, respectively. Twenty-two patients (23%) did not have a history of TIA or stroke. The control group comprised 182 patients without MMA (Table 1). This group consisted of individuals with TIAs (n=41, 22%), ischemic stroke (n=63, 35%), hemorrhagic stroke (n=3, 2%), or various unstable cerebrovascular diseases (n=75, 41%) requiring close monitoring in the stroke care unit in the absence of acute focal deficit (acute artery dissection, reversible cerebral vasoconstriction syndrome). There was no difference in the type of aPL assays used during the study between the 2 groups (Table S1).

The overall prevalence of aPL in patients with MMA was 22%, with 20% having anticardiolipin antibodies (IgG or IgM), 1% anti- β 2GPI (IgG), and 2.0% lupus anti-coagulant (Table 1). Among aPL-positive MMA cases, the prevalence of MMS was 70% (n=15). None of the patients met the diagnostic criteria for antiphospholipid syndrome (APS) according to Sapporo criteria.¹⁰ When comparing the aPL prevalence between MMA and control groups, we found no differences whether the analysis focused on overall aPL positivity or each type of aPL positivity. Additionally, there was no difference between the 2 groups when considering moderate-to-high titers or multiple-positivity profiles.

The subset of patients with MMA with aPL positivity was compared with patients with MMA without aPL regarding cerebrovascular events. The prevalence of TIA, that of ischemic stroke, and that of hemorrhagic stroke did not differ between the 2 groups (Table 2).

Table 2. Cerebrovascular Manifestations in MMA Cases According to aPL Profile

Characteristics	MMA without aPL positivity,* n=74	MMA with aPL positivity,* n=21	P value
Sex, female	51 (69%)	13 (62%)	0.5
Age at test, y	37 (27–42)	37 (32–43)	0.2
Transient ischemic attack	37 (50%)	8 (38%)	0.2
Ischemic stroke	37 (50%)	9 (43%)	0.4
Hemorrhagic stroke	16 (22%)	2 (10%)	0.3

aPL indicates antiphospholipid antibody; IQR, interquartile range; and MMA, moyamoya angiopathy.

*Median (IQR); n (%).

DISCUSSION

The results of this study showed that the prevalence of aPL among patients with MMA was not higher than that observed in the non-MMA group of patients admitted to the stroke care unit. This prevalence is consistent with the frequency of aPL in stroke patients younger than 50 years estimated up to 22% (3%–35%) for anticardiolipin antibodies.¹¹ Interestingly, the majority of aPL-positive MMA cases (70%) had a condition undoubtedly associated with MMA, such as a genetic condition, cranial irradiation, or autoimmune thyroid disease in line with previous results obtained in 17 cases.⁵ Altogether, these findings do not support a causal relationship between aPL and the development of MMA and suggest that the association reported in case studies or small series is essentially coincidental.

None of our patients with MMA with aPL met the clinical and laboratory criteria for APS.¹⁰ Although recent international scientific statements have classified APS as a disorder potentially associated with MMS, most reported cases lacked thrombotic extra-cranial manifestations and did not fulfill APS diagnostic criteria.^{3,5–7,12} APS diagnosis requires the presence of an unexplained thrombotic event, which differs from the brain ischemic event observed in patients with MMA. The only reported case of APS with a definite diagnosis did not meet MMA criteria, as the angiopathy involved only the M2 segment of a single middle cerebral artery.⁴ Therefore, a causal link between APS and MMA seems unlikely.

The prevalence of cerebrovascular events was not higher in patients with MMA with aPL than in those without. This differs from what is observed in patients with aPL in the absence of MMA, where the presence of aPL appears to confer a 5-fold increased risk of stroke or TIA.¹¹ Such a discrepancy may suggest that the cerebrovascular complications of MMA are driven by the intracranial angiopathy regardless of associated prothrombotic factors.

Longitudinal studies are, however, needed to definitively rule out any potential stroke risk of aPL in patients with MMA.

Strengths of this study include the standardized data collection, the relatively large sample size of the MMA sample, the identical tests and analysis period for each group, and the use of the same laboratory for all biological analyses. Potential limitations are the possible biases inherent to a case-control study, the lack of a controlled time period between the clinical events and the sample taken for the assay, the difference in prevalence of clinical events between the 2 groups, and the use of solid-phase assays for the detection of aPL, which is known to exhibit some inter-assay variations.

In conclusion, the results of this study do not support a causal relationship between MMA and the presence of aPL, nor do they support the involvement of aPL in the occurrence of stroke events during the course of the disease.

Sources of Funding

None.

Disclosures

None.

REFERENCES

1. Fujimura M, Tominaga T. Diagnosis of moyamoya disease: international standard and regional differences. *Neurol Med Chir (Tokyo)*. 2015;55:189–193. doi: 10.2176/nmc.ra.2014-0307
2. Barbhaiya M, Zuily S, Naden R, Hendry A, Manneville F, Amigo MC, Amoura Z, Andrade D, Andreoli L, Artim-Esen B, et al; ACR/EULAR APS Classification Criteria Collaborators. 2023 ACR/EULAR antiphospholipid syndrome classification criteria. *Ann Rheum Dis*. 2023;82:1258–1270. doi: 10.1136/ard-2023-224609
3. Oura K, Yamaguchi T, Suzuki T, Yamaguchi Oura M, Itabashi R, Maeda T. Moyamoya syndrome presenting with ischemic stroke caused by rapid worsening of vessel stenosis

associated with triple-seropositive antiphospholipid syndrome. *Intern Med.* 2023;62:793–796. doi: 10.2169/internalmedicine.9316-22

4. Guevara-Rodriguez N, Marmanillo-Mendoza G, Castelar J, Ciobanu C, Fulger I. Unusual presentation of acquired thrombotic thrombocytopenic purpura (TTP) versus catastrophic antiphospholipid syndrome in a patient with Moya-Moya disease, case report, and literature review. *Clin Case Rep.* 2023;11:e7317. doi: 10.1002/ccr3.7317

5. 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;23:1204–1206. doi: 10.1177/0961203314540761

6. Shuja-Ud-Din MA, Ahamed SA, Baidas G, Naeem M. Moyamoya syndrome with primary antiphospholipid syndrome. *Med Princ Pract.* 2006;15:238–241. doi: 10.1159/000092190

7. Yamashita Y, Kusaga A, Koga Y, Nagamitsu S, Matsuishi T. Noonan syndrome, moyamoya-like vascular changes, and antiphospholipid syndrome. *Pediatr Neurol.* 2004;31:364–366. doi: 10.1016/j.pediatrneurol.2004.05.015

8. Herve D, Ibos-Auge N, Calviere L, Rogan C, Labeyrie MA, Guichard JP, Godin O, Kossorotoff M, Habert MO, Lasserre ET, et al. Predictors of clinical or cerebral lesion progression in adult moyamoya angiopathy. *Neurology.* 2019;93:e388–e397. doi: 10.1212/WNL.0000000000007819

9. Devreese KMJ, de Groot PG, de Laat B, Erkan D, Favaloro EJ, Mackie I, Martinuzzo M, Ortel TL, Pengo V, Rand JH, et al. Guidance from the Scientific and Standardization Committee for lupus anticoagulant/antiphospholipid antibodies of the International Society on Thrombosis and Haemostasis: update of the guidelines for lupus anticoagulant detection and interpretation. *J Thromb Haemost.* 2020;18:2828–2839. doi: 10.1111/jth.15047

10. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, Derksen RHW, de Groot PG, Koike T, Meroni PL, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost.* 2006;4:295–306. doi: 10.1111/j.1538-7836.2006.01753.x

11. Sciascia S, Sanna G, Khamashta MA, Cuadrado MJ, Erkan D, Andreoli L, Bertolaccini ML, Action APS. The estimated frequency of antiphospholipid antibodies in young adults with cerebrovascular events: a systematic review. *Ann Rheum Dis.* 2015;74:2028–2033. doi: 10.1136/annrheumdis-2014-205663

12. Gonzalez NR, Amin-Hanjani S, Bang OY, Coffey C, Du R, Fierstra J, Fraser JF, Kuroda S, Tietjen GE, Yaghi S; American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; and Council on Clinical Cardiology. Adult moyamoya disease and syndrome: current perspectives and future directions: a scientific statement from the American Heart Association/American Stroke Association. *Stroke.* 2023;54:e465–e479. doi: 10.1161/STR.0000000000000443