

Predictors of clinical or cerebral lesion progression in adult moyamoya angiopathy

Dominique Hervé, MD, Nathanaelle Ibos-Augé, MD, Lionel Calvière, MD, Christina Rogan, MSc, Marc Antoine Labeyrie, MD, Jean Pierre Guichard, MD, Ophélie Godin, PhD, Manoelle Kossorotoff, MD, PhD, Marie Odile Habert, MD, Elisabeth Tournier Lasserre, MD, Sylvie Chevret, MD, PhD, and Hugues Chabriat, MD, PhD

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Correspondence

Dr. Hervé
dominique.herve@aphp.fr
or Dr. Chabriat
hugues.chabriat@aphp.fr

Abstract

Objective

To identify independent predictors of clinical or cerebral lesion progression in a large sample of adult patients with moyamoya angiopathy (MMA) prior to decisions regarding revascularization surgery.

Methods

Ninety participants (median age, 37.5 years) were assessed at baseline and followed for a median time of 42.8 months. Incident ischemic and hemorrhagic strokes, death, as well as any incident ischemic and hemorrhagic lesions on MRI were recorded. Multiple demographic, clinical, and cerebral imaging measures at baseline were considered as potential predictors of clinical or cerebral tissue change at follow-up. Data were analyzed based on the Andersen-Gill counting process model, followed by internal validation of the prediction model.

Results

Among multiple potential predictive measures considered in the analysis, Asian origin, a history of TIAs, and a reduction in hemodynamic reserve, as detected by imaging, were found to be significantly associated with an increased risk of combined clinical and imaging events. While the model estimated the risk of clinical or cerebral lesion progression to be approximately 0.5% per year when none of these factors was present, this risk exceeded 20% per year when all factors were present.

Conclusion

A simple combination of demographic, clinical, and cerebral perfusion imaging measures may aid in predicting the risk of incident stroke and cerebral lesion progression in adult patients with MMA. These results may help to improve therapeutic decisions and aid in the design of future trials in adults with this rare condition.

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From the Referral Center for Rare Vascular Diseases of the Brain and Retina (CERVCO), Department of Neurology and DHU NeuroVasc (D.H., N.I.-A., C.R., O.G., H.C.), Department of Neuroradiology (M.A.L., J.P.G.), and Laboratoire de Génétique Moléculaire (E.T.L.), Hôpital Lariboisière, Department of Nuclear Medicine, Hôpital Salpêtrière (M.O.H.), and Service de Biostatistique et Information Médicale, Hôpital Saint Louis (S.C.), Assistance Publique des Hôpitaux de Paris; INSERM U 1161 (D.H., E.T.L., H.C.) and UMR 1153 INSERM (S.C.), Université Paris 7 Diderot (E.T.L., H.C.), Sorbonne Paris Cité; Unité Neurovasculaire (L.C.), Hôpital Pierre-Paul-Riquet, Toulouse; Centre National de Référence de l'AVC de l'Enfant, Hôpital Universitaire Necker-Enfants Malades (M.K.), AP-HP; Sorbonne Paris Cité, Paris; and ECSTRA Team (Épidémiologie Clinique et Statistiques pour la Recherche en Santé) (S.C.), Paris, France.

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Glossary

AIC = Akaike information criterion; **ASOL** = arterial steno-occlusive lesions; **AUC** = area under the time-dependent receiver operator characteristic curve; **CBF** = cerebral blood flow; **FLAIR** = fluid-attenuated inversion recovery; **CVR** = cerebrovascular reserve; **HMPAO** = hexamethylpropyleneamineoxime; **IQR** = interquartile range; **MICE** = multiple imputations with chained equations; **MMA** = moyamoya angiopathy; **MMD** = moyamoya disease; **MMS** = moyamoya syndrome; **mRS** = modified Rankin Scale.

Moyamoya angiopathy (MMA) is a rare cerebrovascular disorder characterized by the progressive stenosis of supraclinoid internal carotid arteries and their branches, in association with a network of basal collaterals.¹

Various surgical revascularization techniques are widely applied in children to improve cerebral perfusion and prevent ischemic or hemorrhagic consequences of MMA.^{2–11} Surgical revascularization is also proposed for adult patients.¹² However, little is known about the natural history of MMA in adult patients, although limited data suggest that progression of the disease might be more indolent in adults than in children.¹³ In previous longitudinal studies including adult nonoperated cases, clinical and imaging outcomes were not standardized, the duration of follow-up was limited, or the sample size was small.^{14–19} In addition, therapeutic decisions differ substantially among centers according to the local physician's expertise, experience in revascularization surgery, and explorations used before decision-making. Additional prospective studies are urgently needed to define predictive models that could be used to improve treatment decisions in adults with MMA.

In the present cohort study, we aimed to identify independent predictors of clinical or cerebral lesion progression in a large sample of adult individuals with MMA prior to decisions regarding revascularization surgery.

Methods

This article was prepared according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statements.²⁰

Study design

Among all possible MMA cases referred to the French national referral center for rare vascular diseases of the brain and retina (cervco.fr) between 1999 and 2017, all individuals who satisfied the following criteria were included in the prospective observational study: (1) MMA diagnosed according to the most current definition²¹ and confirmed by both a vascular neurologist (D.H.) and neuroradiologist (M.A.L.), (2) age greater than 16 years, and (3) no history of revascularization surgery and no surgical decision planned at the time of inclusion.

Standard protocol approvals, registrations, and patient consents

Informed consent was obtained for collecting imaging, demographic, and clinical data from each participant, and the

protocol study was approved by an independent ethics committee (Ethics Evaluation Committee of INSERM, reference 17-388).

Data collection

All data were collected from different sources at the individual level and during each visit to the referral center. Data were transmitted electronically according to the best good clinical practice standards using a dedicated electronic case report form.²² A follow-up clinical evaluation was offered to all participants included in the study on a yearly basis at the site of the national referral center. However, follow-up visits to the center were not considered mandatory if it was possible for the patient to see a general practitioner or local neurologist regularly. Data obtained from the MMA cohort were ultimately included in the analysis only when baseline data were followed by at least a second visit with a complete evaluation at the referral center more than 1 year after inclusion.

Collection of baseline and follow-up data

Demographic data (age, sex, ethnic origin, and years of education) and vascular risk factors (previous diagnosis of hypertension with use of an antihypertensive treatment, systolic and diastolic blood pressure, diabetes mellitus, hypercholesterolemia, smoking, and alcohol use) were obtained at study entry. A history of TIAs, defined as focal symptoms lasting <24 hours (presumably of vascular origin); stroke, defined as rapidly evolving focal symptoms lasting ≥24 hours associated with ischemic or hemorrhagic lesions on CT scan or MRI; and seizures or migraine with or without aura were systematically evaluated. Time from the most recent stroke or TIA event to enrollment was recorded, as was the time of first neurologic focal deficit. Disability was also assessed using the modified Rankin Scale (mRS). MMA cases were classified in 2 types, as moyamoya syndrome (MMS) when MMA was associated with specific acquired or genetic conditions and as moyamoya disease (MMD) when MMA was isolated. All patients also received a baseline cerebral MRI that included diffusion-weighted, fluid-attenuated inversion recovery (FLAIR), and T2*-weighted (gradient echo) images. Images were analyzed during dedicated sessions by a vascular neurologist and a neuroradiologist blinded to the clinical status. Only findings recognized by consensus were considered for analysis. The following measures were systematically collected using all imaging data available: (1) presence and location of all potential ischemic or hemorrhagic lesions (recent or old infarcts, subarachnoid hemorrhages, intraparenchymal hemorrhages,

and microbleeds); (2) presence of hyperintense vessels on FLAIR; (3) location of intracranial arterial narrowing or occlusion; (4) presence of moyamoya collateral vessels; (5) presence of transdural anastomosis; (6) narrowing score, corresponding to the sum of arteries (one point for each internal carotid artery, anterior cerebral artery, middle cerebral artery, and posterior cerebral artery), with either stenosis or occlusion (ranging from 0 to 8); (7) Suzuki score obtained from baseline conventional angiography data.

For patients within convenient commuting distance from the referral center, basal and acetazolamide brain perfusion SPECT with ^{99m}Tc -hexamethylpropyleneamineoxime (HMPAO) images, in addition to MRI, were also obtained a few days after the baseline visit, where possible, to evaluate cerebral perfusion and hemodynamic reserve. Two SPECT acquisitions, baseline and post-acetazolamide, were performed with a 48-hour interval. For both acquisitions, participants had an IV line while they rested in a quiet and dimly lit room 10 minutes prior to, during, and at least 5 minutes postinjection of ^{99m}Tc -HMPAO. For the evaluation of hemodynamic reserve, acetazolamide (1 g) was slowly administered via the catheter, 20 minutes before the injection of the radiotracer. The reconstructed slices of both scans were then coregistered, and displayed together. Images were intensity scaled with the cerebellum as reference, namely that for each scan, the maximum value in the cerebellum corresponded to the maximum of the color scale, allowing a visual comparison between basal and post-acetazolamide images. When present, cerebral hypoperfusion at the cortical level was considered severe (level identical to or below white matter cerebral blood flow [CBF] values, more than 50% decrease), moderate (corresponding to a 30%–50% decrease), or mild (close to CBF values in non-affected areas) in the different cerebral lobes. Thereafter, each hypoperfused area on basal SPECT images was assessed based on all MRI parenchymal images available and considered to be related to preexisting cerebral damage (atrophy or obvious infarction or hemorrhage), remote diaschisis secondary to a large cortical lesion, or the direct result of arterial steno-occlusive lesions (ASOL). Alterations in cerebrovascular reserve (CVR) were assessed qualitatively by comparing basal and acetazolamide SPECT images. Intra-observer reproducibility was good ($\kappa = 0.60$) for detecting regional hypoperfusion related to ASOL, and excellent ($\kappa = 0.88$) for recognizing regionally decreased CVR. Interobserver reproducibility was good for both of these measures ($\kappa = 0.76$ and 0.64 , respectively).

During follow-up, a thorough interview of each patient and an analysis of all available medical records were used to collect any incident clinical events, particularly any TIAs or incident strokes. Disability was also assessed using the mRS score. MRI data obtained at baseline and at the last visit to the referral center were also compared to identify any new focal ischemic or hemorrhagic cerebral lesions. The presence of such incidental lesions was confirmed by consensus of 2 different observers. In cases where a decision to perform cerebral

revascularization was made during follow-up, all data obtained from the date of surgery were censored.

Outcomes

As previously reported in other longitudinal studies of rare cerebrovascular disorders,²³ outcome was defined by all clinical and imaging manifestations at the cerebral tissue level suggestive of disease progression; both ischemic and hemorrhagic stroke, death, and any incidental ischemic or hemorrhagic lesions observed during follow-up were considered. The time to occurrence of each event was also defined as a secondary outcome.

Statistical analysis

To obtain the largest sample size of individuals with this rare condition, we considered all MMA patients referred to the center for the present study.

Summary statistics, namely percentages and median values with interquartile ranges (IQRs), were used unless otherwise specified.

The Andersen-Gill counting process model was used for analyzing follow-up data since this model can handle recurrent events and can take into account the correlated, but unspecified, structure of the data.²⁴ The following measures collected at the baseline visit were first considered as potential predictors of clinical or cerebral tissue change at follow-up: age at first symptoms; age at baseline; sex; ethnic origin (Asian, European, or African); MMA type (MMS or MMD); bilateral or unilateral steno-occlusive lesions; various vascular risk factors (hypertension, hypercholesterolemia, diabetes mellitus, alcohol consumption, active smoker); a history of TIAs, ischemic stroke, or hemorrhagic stroke; time elapsed since the last TIA and since the last completed stroke; the presence on MRI of any brain infarct, intraparenchymal hemorrhage, or intravascular hyperintensities; arterial narrowing score; Suzuki score; presence of transdural anastomosis on cerebral angiography; presence of regional hypoperfusion related to ASOL; and alterations in CVR based on SPECT data. First, univariate models were fitted such that all covariates previously reported as risk factors in MMA were considered fixed covariates. Multivariate models were then fitted to predictors selected from univariate analyses at the 10% level (unless the sample included <10 patients), segregating demographic, clinical, MRI, angiographic, and SPECT characteristics. Model selection was based on a stepwise procedure, starting with the full model and removing/adding predictors according to the Akaike information criterion (AIC), and after multiple imputations with chained equations (MICE) of missing data, estimates were averaged over 30 datasets.

Internal validation of the prediction models was based on the Somers Dxy rank correlation, a bias-corrected index, conducted using ordinary nonparametric bootstrapping (150 bootstrap samples) and area under the time-dependent

Table 1 Baseline demographic, angiographic, clinical, MRI, and perfusion measures

	No. (%) or median (IQR)
Age at first symptom, y	32.0 (23–43)
Age at baseline, y	37.5 (29.1–48.7)
Female	63 (70)
Ethnic origin ^a	
European	54 (60)
Asian ^b	12 (13)
African	20 (22)
MMA type	
MMD	54 (60)
MMS	36 (40)
Bilateral	58 (64)
Vascular risk factors	
Hypertension	29 (32)
Hypercholesterolemia	23 (26)
Active smoking	23 (26)
Diabetes mellitus	5 (6)
Alcohol consumption	6 (7)
Main clinical manifestations	
TIAs	43 (48)
Ischemic stroke	39 (43)
Hemorrhagic stroke	15 (17)
Time since last TIA >6 months	10 (23)
Time since last stroke >6 months	8 (21)
MRI measures	
Brain infarct	65 (72)
Intraparenchymal hemorrhage	22 (24)
Microbleed	3 (3)
Intravascular hyperintensities	53 (59)
Angiographic measures	
Arterial narrowing or occlusion score ^c	4 (2–6)
Suzuki score ^d	2 (2–3)
Transdural anastomosis	21/70 (30)
SPECT perfusion measures	
Reduced CVR	14/33 (42)

Table 1 Baseline demographic, angiographic, clinical, MRI, and perfusion measures (*continued*)

	No. (%) or median (IQR)
Reduced arterial steno-occlusion-related perfusion decrease	18/35 (51)

Abbreviations: CVR = cerebrovascular reserve; IQR = interquartile range; MMA = moyamoya angiopathy; MMD = moyamoya disease; MMS = moyamoya syndrome.
Percentages are computed on the entire sample of 90 patients unless specified otherwise.
^a Four individuals originated from South America (n = 2) or had multiple ethnic origin (n = 2). They were not considered in the statistical analysis.
^b An Asian origin was retained for patients originating from East Asia, Southeast Asia, Western Asia, Central Asia, North Asia, or South Asia.
^c Sum of arteries with either stenosis or occlusion (ranging from 0 to 8).
^d Sixteen missing data points.

receiver operator characteristic curve (AUC) as a measure of discrimination.²⁵

The level of significance was set at 0.05 (2-tailed). All analyses were performed using R statistical software version 3.3.2 (R-project.org/).

Data availability

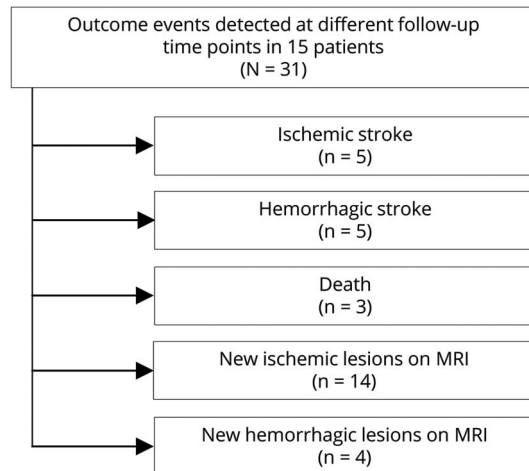
Anonymized data will be shared by request from any qualified investigator for purposes of replicating procedures and results.

Results

Clinical and imaging data at baseline

Among the 113 patients referred with possible MMA during the study period, 90 consecutive cases fulfilled the inclusion criteria and were included in the primary analysis. Seventeen patients were excluded for not meeting eligibility criteria, including 11 MMA diagnosis not confirmed and 6 cases with previous or planned revascularization surgery. Six additional patients with a follow-up less than 1 year were excluded from the analysis. The diagnosis of MMA was confirmed by conventional angiography in 75 cases (83%) and on magnetic resonance angiography combined to cerebral MRI in the remaining 15 participants. Among the 90 patients included in the study, 54 (60%) were diagnosed with MMD and 36 (40%) with MMS. Associated conditions identified in MMS cases included Down syndrome (n = 3), neurofibromatosis type 1 (n = 2), Alagille syndrome (n = 1), MMA related to *PRSS1* gene (n = 1), *GUCY1A3* gene (n = 1), and *BRCC3-MTCPI* genes (n = 1), Graves disease (n = 3), Hashimoto thyroiditis (n = 2), antiphospholipid syndrome (n = 2), intracranial fibromuscular dysplasia (n = 3), and cranial irradiation (n = 1). Sixteen patients were considered as having MMS of unknown etiology because they showed dysmorphic or

Figure 1 Total outcome events



rare malformative features or they had a familial history suggesting a genetic MMS. The main demographic, clinical, and imaging characteristics of the patients included in the study are detailed in table 1. Seventy cases (78%) had a history of cerebrovascular events, 35 complained of recurrent headaches (39%), 10 reported seizures (11%), and 7 (8%) had no previous clinical manifestations of the disease.

Follow-up

The median time to follow-up was 42.8 months (IQR 21.2–65.6 months). Ten strokes occurred in 8 of 90 patients (9%) and were either ischemic (n = 5) or hemorrhagic (n = 5) (figure 1). TIAs were reported by 14 patients (16%) during follow-up. The mRS score increased between baseline and the last follow-up visit in 10 patients; 4 individuals became slightly disabled (mRS 1 or 2); 3 became moderately disabled (mRS 3); and 3 others died (mRS = 6), always after a large intracerebral hemorrhage. Eighteen incident ischemic and hemorrhagic lesions were detected on MRI in 10 and 7 cases, respectively. At the end of the follow-up period, 15 patients (17%) had had a stroke, evidence of ischemic or hemorrhagic lesion on MRI, or had died, accounting for a total of 31 outcome events (figure 1). As shown in figure 2, the hazard of events was relatively constant during the follow-up period. In 10 patients for whom a decision of a surgical revascularization was made (11%), follow-up data were censored from that point.

Predictors

The results of univariate analyses of all demographic, clinical, and potential imaging predictors of clinical deterioration or cerebral tissue changes are detailed in table 2. Based on univariable analyses, 9 predictors—(1) Asian origin, (2) MMD type, (3) presence of bilateral MMA, (4) history of hypertension, (5) previous occurrence of TIA(s), (6) presence of brain infarcts on baseline MRI, (7) arterial narrowing or occlusion score <2 on cerebral

angiography, (8) detection of arterial steno-occlusion-related hypoperfused areas, and (9) decreased CVR on SPECT images—were related to the combination of outcome events (table 2). In the multivariate model, only 3 independent variables—Asian origin, a history of TIA, and reduced CVR—were retained as adding predictive information to each other based on the AIC (table 3).

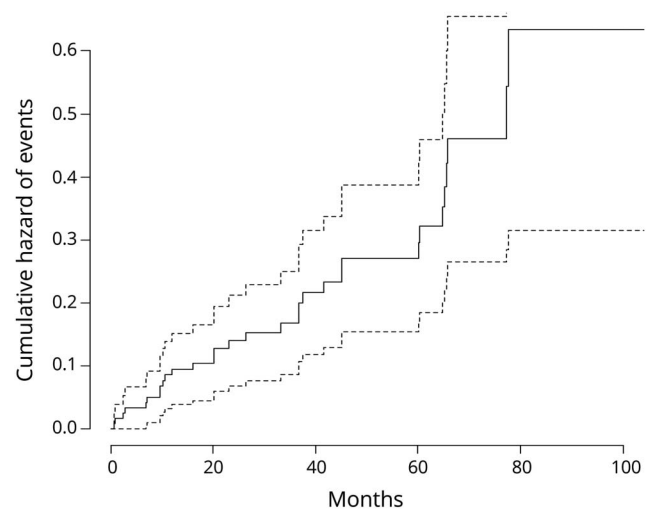
Based on these 3 measures, 8 subsets of patients with different cumulative hazards of events were delineated, as illustrated in figure 3. The 3-year cumulative incidence of events for each of these 8 subgroups is presented in table 4. Patients with none of these 3 predictors had an annual risk of stroke or cerebrovascular lesion of 0.5%; this risk was more than doubled for patients of Asian origin or those with a history of TIAs, and was increased 10-fold when CVR was altered. When all 3 predictors were present, the annual risk was greater than 20% per year.

Internal model validation showed a Somers D value of ~0.65 in both models; that is, when one patient was observed to be free of events compared with another, the patient free of events was 65% more likely to have the lower of the 2 hazard ratios predicted by the model than the patient free of events was to have the higher of the 2 predicted hazard ratios. The AUC showed that the probability that the patient free of events had the lower hazard ratio approached 80% (table 3).

Discussion

In this largest prospective study of MMA ever performed in surgically naive adult individuals, we found that Asian

Figure 2 Observed cumulative hazard of events over time



Note that the hazard of events was relatively constant during the whole follow-up period.

Table 2 Baseline demographic, clinical, MRI, perfusion imaging, and angiographic predictors of clinical deterioration and cerebral tissue changes (univariate models)

	HR (95% CI)	p Value
Age at first symptom >30 years	0.96 (0.47–1.97)	0.91
Age at baseline >40 years	1.33 (0.66–2.70)	0.43
Female	1.13 (0.50–2.56)	0.77
Ethnic origin		
European	1.07 (0.5–2.29)	0.85
Asian	2.70 (1.09–6.68)	0.03
Africa	0.50 (0.17–1.42)	0.19
MMA type		
MMD	1.00	
MMS	10.8 (0.39–1.64)	0.53
Bilaterality	2.5 (0.87–7.18)	0.089
Stroke risk factors		
Hypertension	2.7 (1.26–5.78)	0.01
Hypercholesterolemia	1.28 (0.62–2.65)	0.51
Active smoking	1.15 (0.51–2.58)	0.74
Diabetes mellitus	0.53 (0.07–3.91)	0.53
Alcohol consumption	7.93 (2.81–22.37)	<0.0001
Main clinical manifestations		
Positive history of TIAs	4.75 (1.77–12.74)	0.002
Ischemic stroke	1.09 (0.54–2.21)	0.81
Hemorrhagic stroke	0.39 (0.11–1.38)	0.14
Time since last TIA >6 months	1.23 (0.46–3.29)	0.68
Time since last stroke >6 months	0.85 (0.21–3.39)	0.82
MRI measures		
Brain infarct	4.15 (0.99–17.39)	0.052
Intraparenchymal hemorrhage	1.29 (0.62–2.70)	0.49
Intravascular hyperintensities	0.95 (0.46–1.99)	0.89
Angiographic measures		
Arterial narrowing or occlusion score <2	0.13 (0.02–0.93)	0.042
Suzuki score >3	0.22 (0.03–1.67)	0.14
Transdural anastomosis	0.19 (0.03–1.49)	0.11
SPECT measures		
Hypoperfusion related to ASOL	13.64 (1.74–106.81)	0.013
Reduced CVR	4.06 (1.08–15.33)	0.039

Abbreviations: ASOL = arterial steno-occlusive lesions; CI = confidence interval; CVR = cerebrovascular reserve; MMA = moyamoya angiopathy; MMD = moyamoya disease; MMS = moyamoya syndrome; OR = odds ratio.

origin, a history of TIAs, and detection of regional alterations in cerebral hemodynamic reserve were independently associated with an increased risk of stroke or incidence of cerebral lesions over a median time of 3.6 years. Specifically, our results indicate that, when none of these 3 factors was present, the risk of clinical or cerebral lesions progression was only 0.5% per year, but exceeded 20% per year when all 3 factors were present.

In the present cohort, 3 of 90 individuals died and only 9% of cases had ischemic or hemorrhagic stroke. This frequency is much lower than that previously reported in historical cohort studies of adult MMA patients, in which only a limited number of nonoperated individuals were recruited.^{15–18} However, this value is close to the 10.2% incidence of strokes reported in a recent study of 49 patients that specifically examined the potential predictive value of oxygen extraction fraction over a similar time frame.¹⁴

A history of TIA(s) was associated with a 4-fold increase in the risk of stroke, death, or cerebral lesions in this study. In the general population, the occurrence of TIA(s), which in most cases result from a transient intracranial artery occlusion caused by an embolism or in situ thrombotic occlusion, represents a major risk for subsequent ischemic stroke.^{26,27} In MMA patients, TIAs may essentially result from a transient, but profound, decrease in blood supply downstream of chronic steno-occlusive arterial lesions when the limits of autoregulation are exceeded.²⁸ Thus, any potential source of vasoconstriction at the cerebral level (e.g., decrease in CO₂ partial pressure due to hyperventilation with crying or exertion) or reduction in blood pressure (e.g., in association with induction of anesthesia or use of antihypertensive agents) can promote the ischemic manifestations frequently observed in patients with MMA.²⁹ A completed ischemic stroke might represent the ultimate and final consequence of this process, which could explain why TIAs, but not ischemic strokes, were associated with the incidence of stroke events in our cohort. Notably, patients with recent TIAs were not at higher risk than those with TIAs that occurred more than 6 months previously, suggesting that TIAs may remain a good predictor of stroke events over a long time frame in MMA.

In line with this interpretation, we also observed that a reduction in CVR³⁰ caused a 4-fold increase in the risk of clinical worsening or incidence of cerebral tissue changes. It was previously reported that the regional oxygen extraction fraction, which presumably increases at the cerebral tissue level when autoregulation is exceeded,³¹ does not predict stroke incidence in patients with MMA.^{14,32} The limited number of patients included in these studies, low event rate, rare prevalence of high oxygen extraction fraction, and large number of censored cases due to the decision to pursue revascularization surgery might explain

Table 3 Multivariate analysis after multiple imputation of missing data and implementation of a backward selection procedure

Significant predictors	HR (95% CI)	p Value	Validation tests	Values
Asian	2.63 (1.00–6.94)	0.051	Somers D	0.640
TIA	4.18 (1.37–12.75)	0.012	R ²	0.340
Reduced CVR	4.40 (1.20–16.10)	0.026	60-month AUC	0.788

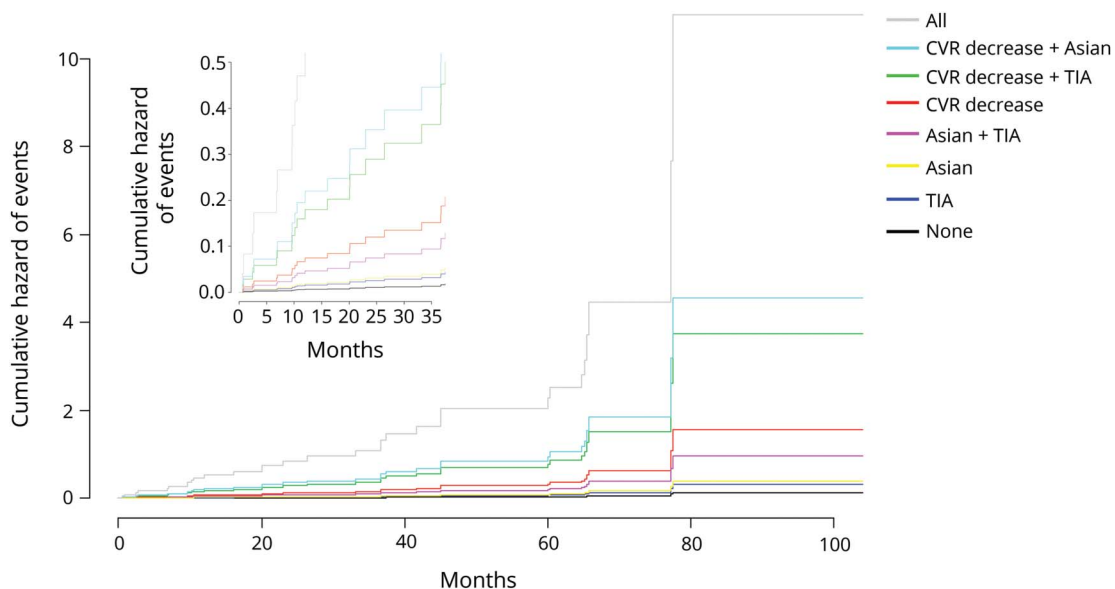
Abbreviations: AUC = area under the time-dependent receiver operator characteristic curve; CI = confidence interval; CVR = cerebrovascular reserve; HR = hazard ratio.

these negative results. In the present study, a decrease in CVR had a predictive value independently of TIAs, which are also presumably related to hemodynamic alterations. This suggests that alterations in CVR might be detected prior to or in the absence of any transient ischemic clinical manifestations. Alternatively, TIAs might also result from cerebral tissue dysfunction in areas distinct from the location whereas CVR decrease was detected by SPECT-based measurements of CBF. Most importantly, the results obtained in this cohort also show that the combination of TIA(s) and a reduction in CVR considerably increases the risk of clinical worsening or the incidence of cerebral lesions, which were estimated to be greater than 10% per year at the individual level. Taken together, these findings emphasize that the presence of regional CVR alterations, which can, but not necessarily do, translate into transient focal symptoms, is of the utmost importance for evaluating the risk of clinical or cerebral lesion progression in MMA.

The number of outcome events was too low to evaluate whether a history of TIAs or a decrease in CVR has the same predictive value for ischemic and hemorrhagic events. However, accumulating evidence suggests that hemodynamic failure at the cerebral level promotes not only ischemic but also hemorrhagic lesions. In particular, it has been found that long-term hemodynamic stress to collateral vessels is capable of altering vascular wall structure, leading to cerebral hemorrhage.^{1,33} In keeping with this, cerebral revascularization after extracranial–intracranial bypass surgery, which decreases this phenomenon,³⁴ prevents not only ischemic but also hemorrhagic manifestations of the disease.³⁵

Asian origin was also independently predictive of the incidence of stroke, cerebral lesions, or death in our MMA patient cohort, though its prognostic value was decreased in the multivariable models, suggesting some levels of confounding. Nevertheless, this was in agreement with

Figure 3 Cumulative hazard of events over time predicted by the model



A zoom of the cumulative hazard of events during the 35 first months of follow-up is shown in the center of the panel. CVR = cerebrovascular reserve.

Table 4 Estimated risk event at 3 years, according to multiple combinations of predictive factors (from smallest to largest values)

	Risk event at 3 years, %
No predictive factor	1.5
Previous TIAs	3.5
Asian origin	4.3
Asian origin and previous TIAs	10
Reduced CVR	15.6
Reduced CVR and previous TIAs	33.5
Asian origin and reduced CVR	39.2
All predictive factors	69.9

Abbreviation: CVR = cerebrovascular reserve.

previous findings. Indeed, in 2 large MMA series, it was previously reported that ethnicity is an important determinant of prognosis.¹³ Recently, the R4810K variant of ring finger protein 213 (RNF213) was found to be strongly associated with MMD in both Japanese and Korean patients, and to a much lesser degree in Chinese patients.³⁶ This variant is not associated with MMD in Caucasian individuals.³⁷ Additional investigations are needed to determine whether the worse prognosis associated with an Asian origin is related to genetic differences that influence the progression of cerebral arterial lesions in MMA or to another cause.

Female sex and Suzuki score were not found independently associated with an increased risk of stroke or incidence of cerebral lesions. These results contrast with what previous studies suggested.^{38–40} This may be due to the cohort size and to a lack of power.

Specific strengths of this study include the prospective design of standardized data collection for this rare condition in a European referral center, the relatively large sample size and long evaluation period without a surgical revascularization decision, the centralized data management, and strong internal validation of the prediction model.

There are also several potential limitations. The recruitment period was long, and intervals between follow-up visits were variable owing to multiple logistical constraints. Moreover, the number of events was relatively low and variable at the individual level. However, we used the Andersen-Gill counting process model, which allows consideration of both multiple events within subjects and the discontinuous structure of the data. To increase the power to detect predictors in such a cohort, we also selected patients independently of their MMA etiologic

subtypes and considered both clinical and imaging events as outcomes. Etiologic heterogeneity did not seem to have a major role in predicting outcomes in our dataset, but cannot be excluded. Hemodynamic status evaluation using SPECT was not performed in the whole cohort. We used, because of this specific limitation, a model selection including MICE of missing data. In this study, we retained an Asian origin not only for patients originating from East Asia, but also for patients originating from other subregions of this continent. Additional studies would be needed to confirm these results in patients originating from East Asia. A larger sample would also be needed to confirm these results based only on clinical manifestations. In addition, although an internal validation was performed, our prediction model was not externally validated using independently collected data from a different source. Finally, participants with a history of surgical revascularization were not included in this study. This selection criterion might have underestimated the risk of events, since only patients with a less severe condition would have been selected. However, only 6/113 (5.3%) patients screened for inclusion were ultimately excluded because of planned or previous revascularization surgery, and most of the enrolled cases were symptomatic and had a history of TIA(s), or ischemic or hemorrhagic stroke at baseline.

This study clearly demonstrates that a simple combination of demographic, clinical, and imaging markers may aid in predicting the risk of clinical worsening and cerebral tissue changes in adult patients with MMA. The information provided by these results is important for improving the management of MMA in adult patients, particularly regarding therapeutic decisions, as well as for designing future therapeutic trials in this rare condition.

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Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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Appendix Authors

Name	Location	Role	Contribution
Dominique Hervé, MD	University Hospital Lariboisière, Paris, France	Author	Contributed to the protocol development, study design and concept, conduct, data acquisition, and coordination, data interpretation, writing and reviewing of the report
Nathanaelle Ibos-Augé, MD	University Hospital Lariboisière, Paris, France	Author	Involved in data interpretation and writing the first draft
Lionel Calvière, MD	University Hospital Pierre-Paul-Riquet, Toulouse, France	Author	Involved in data acquisition and revising the report
Christina Rogan, MSc	University Hospital Lariboisière, Paris, France	Author	Involved in study conduct and data acquisition
Marc Antoine Labeyrie, MD	University Hospital Lariboisière, Paris, France	Author	Involved in data acquisition and revising the report
Jean Pierre Guichard, MD	University Hospital Lariboisière, Paris, France	Author	Involved in data acquisition and revising the report
Ophélie Godin, PhD	University Hospital Lariboisière, Paris, France	Author	Designed and executed the statistical analysis
Manoelle Kossorotoff, MD, PhD	University Hospital Necker Enfants Malades, Paris, France	Author	Involved in study conduct, data acquisition, revising the report
Marie Odile Habert, MD	University Hospital Pitié Salpêtrière, Paris, France	Author	Involved in study conduct, data acquisition, revising the report
Elisabeth Tournier Lasserre, MD	University Hospital Lariboisière, Paris, France	Author	Involved in data interpretation and revising the report critically
Sylvie Chevret, MD, PhD	University Hospital Saint-Louis, Paris, France	Author	Designed and executed the statistical analysis, wrote the first draft of the statistical analysis, reviewed the report
Hugues Chabriat, MD, PhD	University Hospital Lariboisière, Paris, France	Author	Involved in study design and concept, data interpretation, critical revision, reviewing the report

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