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Progression of Unilateral Moyamoya Disease: A Clinical Series

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Key Words
Moyamoya disease · Contralateral anterior cerebral artery · Bilateral stenosis

Abstract
Background: The natural history of unilateral moyamoya disease (MMD) in adult patients is not clearly described in the literature. We present a series of 18 patients with unilateral MMD and analyze the risk factors for progression to bilateral disease. ***Methods:*** A retrospective review of 157 MMD patients treated at Stanford University Medical Center from 1991 to 2005 identified 28 patients with unilateral MMD (defined as none, equivocal or mild involvement on the contralateral side). ***Results:*** Eighteen patients (5 males and 13 females) were identified with unilateral MMD and angiographic follow-up of ≥5 months. Mean radiologic follow-up (± standard error of the mean) was 19.3 ± 3.4 months and mean clinical follow-up was 24.5 ± 3.7 months. Five patients had childhood onset MMD and 13 patients had adult onset disease. Angiographic progression from unilateral to bilateral disease was seen in 7 patients (38.9%) at a mean follow-up of 12.7 ± 2.4 months. Four of the 7 patients had significant clinical and radiologic progression requiring surgical intervention. Five of 7 patients that progressed had adult onset MMD. The presence of equivocal or mild stenotic changes of the contralateral anterior cerebral artery (ACA), middle cerebral artery (MCA) or internal carotid artery (ICA) was an important predictor of progression ($p < 0.01$); 6 of 8 patients (75%) with equivocal or mild contralateral disease progressed, whereas only 1 of 10 patients (10.0%) with no initial contralateral disease progressed to bilateral MMD. One patient had mild or equivocal MCA, ICA and ACA stenosis at the time of initial diagnosis and this patient progressed. ***Conclusions:*** Contralateral progression in the adult form occurs more commonly than previously reported. The presence of minor changes in the contralateral ACA, intracranial ICA and MCA is an important predictor of increased risk of progression. Patients with a completely normal angiogram on the contralateral side have a very low risk of progression.

Introduction

Moyamoya disease (MMD) has an unknown etiology and was originally described by Suzuki and Kodoma [1] and Suzuki and Takaku [2]. It is characterized by progressive bilateral stenosis or occlusion of the internal carotid artery (ICA) with the formation of a vascular network, the so called 'moyamoya vessels'. Moyamoya syndrome has the same angiographic appearance but is associated with other medical conditions such as Down syndrome,

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neurofibromatosis type 1 (NF-1), previous radiation therapy, head trauma, meningitis, autoimmune disease and arteriosclerosis [3].

The Research Committee on Spontaneous Occlusion of the Circle of Willis (Moyamoya Disease) of the Ministry of Health and Welfare, Japan, defines adult 'definite' MMD as bilateral stenosis or occlusion of the terminal portion of the ICA and/or at the proximal portion of the anterior (ACAs) and/or middle cerebral arteries (MCAs) seen on cerebral angiography or magnetic resonance angiography [3]. The progression of the contralateral side in patients with predominantly unilateral adult MMD remains unclear. Angiographic risk factors that relate to this progression are not clearly understood either. This study examines patients with unilateral MMD and moyamoya syndrome for predictors of progression on the contralateral side.

Materials and Methods

All patients with unilateral MMD treated surgically by the senior author (G.K.S.) at Stanford University Medical Center were included in the study. The study period was from 01 January 1991 to 31 December 2005. A total of 157 surgically treated patients with MMD were analyzed to identify 28 patients with the diagnosis of unilateral MMD. Unilateral MMD was defined angiographically when there was unilateral stenosis or occlusion of the ICA, ACA or MCA and the formation of moyamoya vessels, with none, equivocal or mild stenosis on the contralateral side. The angiograms were interpreted by two neuroradiologists (M.P.M. and H.M.D.). When moderate or severe contralateral disease was present, the patients were considered to have bilateral disease and were excluded from the study. Adequate clinical and angiographic follow-up was defined as ≥ 5 months in duration.

Patients with angiographically proven MMD and the presence of Down syndrome, NF-1 and previous radiation therapy were included to study the risk of developing bilateral disease in this subgroup. Both pediatric and adult patients were included in the study.

The study patients were divided into 2 groups. Group 1 patients had contralateral progression and group 2 patients did not have contralateral progression. A comparison of groups 1 and 2 was performed to identify any risk factors for progression to bilateral MMD. Progression was defined as the time from initial diagnosis to either the last follow-up angiogram in patients that did not require surgical treatment or to the date of surgical treatment if required.

All patients had digital subtraction angiography (DSA) at the time of initial diagnosis. Follow-up imaging was performed using DSA in all patients.

Statistical Analysis

Categorical variables were analyzed using the χ^2 test to identify risk factors between groups 1 and 2 for contralateral progression. Differences were considered statistically significant if the p value was <0.05. Continuous variables were expressed as mean ± standard error of the mean, range and percentage.

Results

Patient Characteristics

Twenty-eight patients with a diagnosis of unilateral MMD were identified. Clinical and angiographic follow-up of ≥ 5 months was available in 18 patients. There was no difference in baseline characteristics between the 10 patients that were excluded and the 18 patients in the final series. Of the 10 patients excluded, 5 patients were treated within the previous 5 months and therefore had less than 5 months of angiographic follow-up. No radiologic follow-up could be obtained in 3 patients. Two patients with follow-up magnetic resonance angiography (MRA) were excluded. Mean clinical follow-up was 24.5 ± 3.7 months (range 5–60). Contralateral progression was identified in 7 patients (group 1); no progression was identified in 11 patients (group 2). The average age of the study group (groups 1 and 2) was 29.8 ± 3.5 years (range 2–52). Thirteen patients were females and 5 patients were males. Five patients were classified as having pediatric MMD (0–18 years) and 13 patients had adult MMD.

Mean angiographic follow-up was 19.3 ± 3.4 months (range 5–60). All patients underwent conventional DSA at the time of diagnosis and for follow-up. All patients had initial severe stenosis or occlusion of the ICA or MCA with formation of moyamoya vessels on the ipsilateral side. None of the patients had only ACA stenosis, because this angiographic finding was not considered significant enough to warrant surgical intervention at our institution.

Thirteen of the patients presented with ischemic symptoms; 6 patients had strokes and 7 had transient ischemic attacks. Two patients presented with hemorrhage and 3 patients with intractable headaches. None of the patients were asymptomatic. All patients that progressed initially presented with ischemic symptoms (n = 6) or hemorrhage (n = 1).

Surgical management was performed in all patients after the initial diagnosis because of decreased cerebral blood flow and/or impaired hemodynamic reserve to the affected side. Direct superficial temporal artery to MCA bypass was performed in 14 patients. Three pediatric patients (patients No. 13, 14 and 18) and 1 adult patient (patient No. 9) underwent unilateral encephaloduromyosynangiosis because of inadequate artery size for direct revascularization. Baseline patient characteristics are summarized in table 1.

Comparison of Groups 1 and 2

Progression was noted in 7 of the 18 patients (38.9%). Patient characteristics analyzed were sex, age, pediatric

Table 1. Baseline patient characteristics

Patient	Age years	Sex	Presenting symptom	Total duration of clinical follow-up, months	Progression	Time to progression months	Initial equivocal or mild contralateral involvement	GOS
1	34	M	TIA	48	yes	15	A1, ICA, M1	5
2	50	F	TIA	60			ICA	5
3	37	M	TIA	33	yes	8	ICA	5
4	17	F	infarction	36	yes	8		5
5	31	F	TIA	26				5
6	49	M	TIA	18				5
7	23	F	headache	12			ICA	5
8	10	F	infarction	8				5
9	45	F	ICH	5	yes	5	A1	5
10	28	F	TIA	18	yes	12	A1	5
11	28	F	headache	10				5
12	21	F	TIA	5				5
13	15	F	infarction	18				5
14	2	F	infarction	5				5
15	41	M	ICH	32				4
16	39	F	headache	23				5
17	52	F	infarction	24	yes	22	A1	5
18	14	M	infarction	19	yes	19	A1	5

GOS = Glasgow outcome score; TIA = transient ischemic attack; ICH = intracerebral hemorrhage.

Table 2. Comparison of groups 1 and 2

	Group 1	Group 2
Cases	7	11
Female:male	4:3	9:2
Pediatric patients (0–18 years)	2	3
Ethnicity	Caucasian 5, Asian 2	Caucasian 5, Asian 5, Hispanic 1
Angiographic follow-up, months		
Mean ± SEM	17.1 ± 3.5	19.0 ± 3.3
Range	5–33	5–60
Presence of equivocal or mild contralateral changes*	6/7	2/11
Associated disease	Down syndrome (n = 1)	NF-1 (n = 2), prior radiation (n = 1)

Group 1 patients progressed, group 2 patients did not progress.
* Statistical significance of $p < 0.05$.

onset, ethnicity, follow-up period, presence of initial contralateral minor angiographic changes and the presence of associated diseases such as NF-1, Down syndrome and previous radiation.

Group 1 had 4 females and 3 males while group 2 had 9 females and 2 males. There were 2 pediatric patients that progressed (patients No. 4 and 18). None of the 3 other pediatric patients were noted to have progressed at a mean follow-up of 10.3 ± 3.9 months (range 5–18).

Group 1 patients had a mean radiologic follow-up of 17.1 ± 3.5 months (range 5–33), and group 2 patients had a mean radiologic follow-up of 19.0 ± 3.3 months (range 5–60).

The comparison of groups 1 and 2 is shown in table 2.

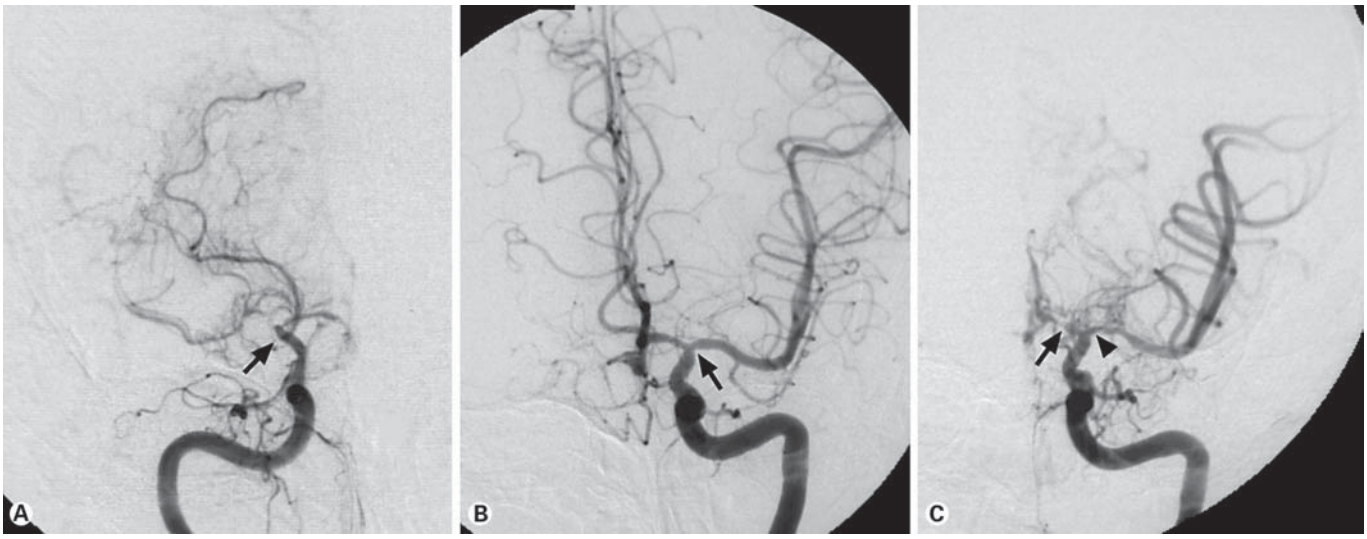

Fig. 1. A Initial anteroposterior digital subtraction angiogram on the side of treatment from patient No. 1. It shows occlusion of the distal right ICA (arrow), MCA (M1) and ACA (A1) and the formation of collateral moyamoya vessels. **B** Initial anteroposterior digital subtraction angiogram on the contralateral side from patient No. 1 showing mild narrowing of the distal left supraclinoid ICA (arrow), proximal MCA and equivocal narrowing of the proximal A1. **C** Follow-up anteroposterior digital subtraction angiography from patient No. 1 showing severe progression in 15 months with the development of high-grade stenosis of the distal left ICA, MCA (M1) (arrowhead) and ACA (A1) (arrow) and the formation of collateral moyamoya vessels.

Angiographic Risk Factors for Progression

The only significant difference noted in the comparison of groups 1 and 2 was the presence of equivocal or mild contralateral angiographic changes at the time of initial diagnosis ($p < 0.01$). A total of 8 of the 18 patients (44.4%) had evidence of equivocal or mild contralateral stenosis. Progression was seen in 6 of these 8 patients (75%). One of the 10 patients (10.0%) with no contralateral disease developed subsequent contralateral stenosis. The initial angiograms were all interpreted by experienced neuroradiologists (M.P.M. or H.M.D.). There were no collateral moyamoya vessels noted on the contralateral side.

One major risk factor for progression identified was equivocal or mild changes in the contralateral A1 segment of the ACA. Five of the 7 patients that progressed had contralateral A1 involvement at the time of initial diagnosis, 1 had contralateral mild ICA stenosis and 2 had a normal angiogram. In contrast, there was no A1 disease seen in any of the 11 patients that did not progress. Three of the 5 patients that had A1 disease developed severe contralateral progression that required surgical revascularization.

Contralateral equivocal or mild ICA stenosis was seen in 4 patients in the study. Two of these patients developed progression (patients No. 1 and 3) and 1 required treatment (patient No. 1).

One patient had MCA involvement at initial diagnosis (patient No. 1). He had equivocal or mild M1, A1 and ICA stenosis noted on angiography (fig. 1). There was no association between the presence of posterior circulation stenosis and the development of progression.

One patient developed contralateral stenosis without prior evidence of any earlier contralateral changes (patient No. 4). Patient No. 4 was a 17-year-old female with Down syndrome who developed progression to severe left MCA stenosis by 8 months. She was subsequently treated with a contralateral superficial temporal artery to MCA direct bypass procedure. The characteristics of group 1 patients are shown in table 3.

Time to Progression and Development of Contralateral Symptoms

The time to progression which is defined as the period from initial diagnosis to either the last angiogram in nonsurgical patients or contralateral surgery was 12.7 ± 3.5 months (range 5–22) in the 7 patients. There was no significant difference regarding the time of follow-up between groups 1 and 2. Progression to severe contralateral ICA stenosis was seen in 4 patients (patients No. 1, 4, 10 and

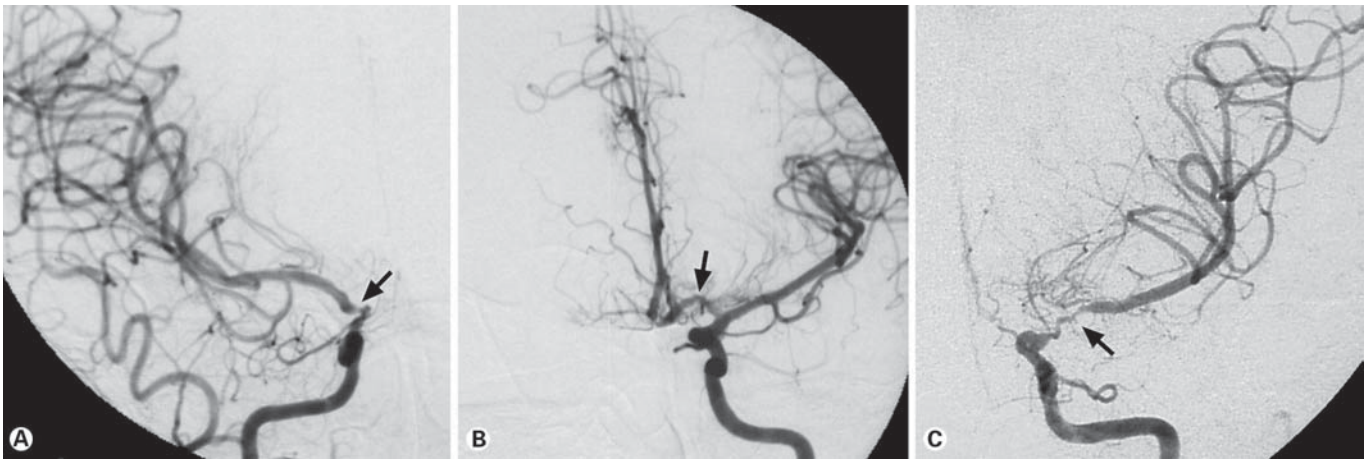

Fig. 2. A Initial anteroposterior digital subtraction angiography from patient No. 17 on the side of treatment showing occlusion of the right ACA (A1) and severe stenosis of the MCA (M1) (arrow). **B** Initial anteroposterior digital subtraction angiography on the contralateral side from patient No. 17 showing mild left A1 disease (arrow). **C** Follow-up digital subtraction angiography from patient No. 17 showing the development of severe left MCA disease (arrow), occlusion of the left ACA (A1) and moyamoya vessel formation at 22 months of follow-up.

Table 3. Characteristics of group 1 patients

Patient	Age years	Sex	Angiographic changes on the contralateral side at time of initial diagnosis	Time to progression months	Symptoms on the side of progression	Severity of angiographic progression	Treatment on the side of progression	Presence of associated conditions
1	34	M	equivocal left A1 ACA, M1 MCA and ICA stenosis	15	none	severe	left STA-MCA	
3	37	M	equivocal right ICA stenosis	8	none	moderate	none	
5	17	F	normal	8	none	severe	left STA-MCA	Down syndrome
10	45	F	equivocal left A1 ACA stenosis	5	none	moderate	none	
12	28	F	mild left A1 ACA stenosis	12	none	severe	left STA-MCA	
17	52	F	mild left A1 ACA stenosis	22	TIA	severe	left STA-MCA	
18	14	M	mild left A1 stenosis	19	none	mild	none	

STA-MCA = Superficial temporal artery to MCA bypass procedure; TIA = transient ischemic attack.

17) over an average follow-up of 14.3 months (range 8–22). Three patients (patients No. 3, 9 and 18) had moderate progression on the contralateral side that was not considered severe enough for surgical revascularization at last follow-up (33, 5 and 19 months, respectively). Six patients that progressed were asymptomatic and 1 patient (patient No. 17) developed a contralateral transient ischemic attack during follow-up which prompted surgical intervention (fig. 2). The 4 patients with severe angiographic progression underwent contralateral superficial temporal artery to MCA direct bypass procedures without complications.

Discussion

Unilateral MMD is an uncommon condition and is especially rare in adults. A recent literature review by Kusaka et al. [4] included 20 papers that identified 173 patients with unilateral MMD. The Research Committee on Spontaneous Occlusion of the Circle of Willis of the Ministry of Health and Welfare, Japan, classifies these patients as 'probable' MMD [3]. Other classifications include 'quasi-moyamoya disease', 'akin-moyamoya disease', 'moyamoya syndrome' and 'moyamoya phenomenon' [3]. We

included all patients with classic angiographic findings of unilateral MMD in this study, i.e. patients with associated diseases such as NF-1, Down syndrome and previous radiation therapy. We feel it is important to include all patients in this study because the natural history of patients with unilateral disease is not well described.

ACA, MCA and ICA Stenosis as an Indicator of Risk of Contralateral Progression

In this series, the presence of equivocal or mild stenosis of the contralateral A1 segment of the ACA, M1 segment of the MCA or ICA was a good predictor of risk of contralateral progression. Six of 8 patients with contralateral ACA, MCA or ICA changes progressed, compared with only 1 of 10 patients with normal contralateral angiography. Equivocal or mild contralateral A1 stenosis was seen in 5 of the 7 patients that progressed contralaterally. Of the 5 patients with ACA stenosis, 3 developed severe contralateral involvement and 2 developed moderate contralateral disease. Contralateral ACA stenosis, even if very mild, may be an important predictor of progression because it likely represents an early sign of bilateral disease. It is important to carefully assess the contralateral vessels for even very minor involvement, and if present, follow this subgroup closely. ACA involvement is often difficult to differentiate from a hypoplastic A1 segment of the ACA which is a normal anatomical variant. Therefore, serial angiography should be performed to assess change. At our institution, we follow all patients that have possible contralateral changes or hypoplastic A1 segments with serial angiography every year to rule out progression.

Only 1 patient (patient No. 1) had angiographic evidence of mild M1 disease on the contralateral side at the time of initial diagnosis. A digital subtraction angiogram of patient No. 1 is shown in figure 1B. No statistical correlation can be made between the presence of contralateral mild or equivocal MCA disease and the risk of progression. However, we believe that MCA stenosis on the contralateral side is likely as strong a predictor of progression as ICA or ACA stenosis.

It was also noted in this series that 10 patients had no involvement of the opposite side at initial diagnosis. Only 1 of these patients progressed. This patient had pediatric onset MMD and Down syndrome. We believe that this patient was at a higher risk of progression because she had Down syndrome [5]. We conclude that a completely normal angiogram on the contralateral side is an excellent predictor that progression is unlikely in the adult patient.

Progression in Adults with Unilateral Involvement

There is a paucity of literature describing the risk of progression in adult patients. Hirotsune et al. [6] reported a series of 17 patients with unilateral MMD with long-term follow-up. Progression was seen in 6 of the 12 pediatric patients but in none of the 5 adult patients. The low risk of progression in the adult subgroup is in contrast to our series where 5 of 13 (38.5%) adult patients progressed. Although the numbers are small, 2 of the 5 (40%) pediatric patients progressed. There was no significant difference in the rate of progression between adult and pediatric patients. These data emphasize the importance of close follow-up in both adult and pediatric MMD patients.

A series of 10 patients by Houkin et al. [7] examined progression in 6 adult and 4 pediatric patients with unilateral MMD. None of the 6 adult patients had progression on the contralateral side during a mean follow-up of 4.3 years (range 2–8). We believe there may be a distinct nonprogressive form of unilateral MMD but it is often difficult to identify these patients. Consequently, all patients warrant close follow-up.

A recent study by Kuroda et al. [8] examined the progression of MMD in both bilateral and unilateral cases of adult MMD. They identified 11 patients with unilateral MMD. Progression was seen in 4 (36.4%) of these patients at a mean follow-up of 5 years (range 1.5–8.0). All 4 of the patients that progressed were females. Female gender was the only significant risk factor for progression in their study. In the present study, female gender was not a significant risk factor for progression in unilateral cases, but contralateral minor changes did increase the risk of progression. The study by Kuroda et al. [8] did not examine angiographic risk factors. They concluded that patients with unilateral MMD may have a higher risk of progression than previously thought [8]. Female gender and minor angiographic changes are likely two risk factors for progression in unilateral patients.

Only 7 of the 18 patients in our series had an Asian background. Five of the patients that progressed were Caucasian and 2 were Asian. It is possible that unilateral adult MMD in Caucasian patients behaves more aggressively than in Asian patients. Thus, the presentation and natural history of MMD may have racial and geographic variations. Further study is needed to confirm this hypothesis.

Duration to Progression

The duration to progression of unilateral MMD is unclear. Hirotsune et al. [6] reported a mean time to devel-

oping contralateral lesions of 6.2 years. In the series of Houkin et al. [7], the pediatric patients developed progressive contralateral disease at a mean follow-up of 3.1 years (range 0.5–7). These reports are in contrast to our series where 7 patients developed contralateral progressive lesions by 12.7 ± 3.5 months (range 5–22). Our follow-up period is not as long as the study of Hirotsune et al. [6] or Houkin et al. [7], but our study has a different racial composition that may contribute to a more aggressive disease progression. In our series, none of the pediatric patients had contralateral angiographic abnormalities at the time of initial diagnosis. Pediatric patients with unilateral disease may have a longer delay until progression than adult patients, but further study is needed to clarify this difference.

Limitations of the Current Study

The current study is limited by the relatively short follow-up of 5 months in 3 of the patients and its retrospective design. The mean follow-up for the entire group is just over 2 years. Longer follow-up may show an increased rate of progression in the unilateral moyamoya patients with no evidence of contralateral disease.

The patients are a surgical cohort. Selection bias may exist if these patients have a higher risk of progression than patients that do not require surgical treatment.

It is unclear why only 1 pediatric patient had contralateral angiographic changes at the time of initial angiography. The small sample size makes statistical analysis difficult. In this series, 2 of 5 (40.0%) pediatric patients developed progression. There was no significant difference in the rate of progression between adult and pediatric patients.

The true definition of unilateral disease is unclear as 8 of the patients had equivocal or mild disease on the contralateral side. The presence of these equivocal or mild changes on the contralateral side may represent a variant of bilateral disease. These patients were studied because the natural history of patients with this finding has not been well described.

Finally, the total series comprised 28 patients, but adequate angiographic follow-up was obtained in 18 patients (64.3%). This may introduce errors to the study. Five of 28 (17.9%) patients were excluded because they were treated recently and had less than 5 months follow-up. Three of 28 patients (10.7%) did not have any angiographic follow-up. Two patients were excluded because they only had MRA follow-up and we are unsure of the sensitivity of MRA for detecting mild progression.

Conclusions

This study has shown that unilateral patients with contralateral equivocal or mild ACA and ICA changes are at an increased risk of progression. In contrast, unilateral MMD patients with a completely normal angiogram on the contralateral side have a very low risk of progression.

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