Moyamoya Disease in Europeans

Markus Kraemer, MD; Wilhelm Heienbrok, MD; Peter Berlit, MD

Background and Purpose—We describe the clinical, diagnostic, and outcome features of a cohort of white patients with idiopathic moyamoya disease treated in a German institution.

Methods—Our cohort included 21 white patients with moyamoya disease. Clinical and diagnostic features were obtained by retrospective chart review; follow-up information and outcome were obtained prospectively. We used the Kaplan–Meier methods to estimate stroke risk by treatment status.

Results—The mean age at onset of symptoms was 31 years. The female predominance was 4.25:1. In our cohort, the initial symptom was a cerebral ischemic event in all patients. There was no patient with a hemorrhage at onset; only one patient experienced subarachnoidal hemorrhage in the further course of disease. The Kaplan–Meier risk for recurrent stroke was very high after the first ischemic event and smaller after angiographic diagnosis. The 5-year-Kaplan–Meier risk of recurrent stroke was 80.95% after the first ischemic event for all patients. Most subsequent ischemic events appeared in the first 2 years after symptom onset. Eleven patients (52.3%) underwent neurosurgical revascularizing procedures. After surgery, the Kaplan–Meier risk of perioperative or subsequent stroke was 27.27% within the first month and was stable thereafter.

Conclusion—Clinical features and course of moyamoya disease of whites analyzed in this German study are comparable to American results. Moyamoya disease in whites differs clearly from Asian moyamoya disease in timing of onset of vasculopathy and lower rate of hemorrhages. (Stroke. 2008;39:3193-3200.)

Key Words: moyamoya disease ■ Europeans ■ revascularizing procedure ■ nonsurgical treatment

Moyamoya disease (MMD) is a rare idiopathic occlusive cerebrovascular disorder characterized by progressive stenosis or occlusion of the distal internal carotid artery and proximal cerebral arteries with an extensive network of cerebral collaterals. First described in 1957 by Takeuchi and Shimizu, Suzuki and Takaku named the disease after the Japanese term “moyamoya” in 1969. The appearance of the abnormal fine vascular network in catheter angiography was described as “a hazy cloud like a puff of cigarette smoke.” MMD as an idiopathic vasculopathy has to be differentiated from moyamoya syndrome as an angiographic correlate of other basic disease entities such as trisomy 21, neurofibromatosis, and arteriosclerosis.

Remarkable regional and racial differences exist in the frequency of MMD in the world. This disease is mostly found in Asians, especially in Japan and Korea. Although the estimated prevalence in the entire Japanese population is ≥3 per 100 000 persons, the disease is extremely uncommon in non-Asian populations.

Reviewing the literature, one realizes that there is only very rare data about MMD in whites. Limited data suggest notable differences in presentation and course of the disease. In 1998, Chiu et al reported 22 white Americans with MMD and described several differences between disease presentation in the United States and in Japan. Another white MMD cohort with 23 white Americans was reviewed by Hallemeier et al in 2006. Recent authors have emphasized the lack of data regarding the characteristics and natural course of this condition in European whites. The limited existing European studies mostly deal with a mixed cohort of MMD and angiographic syndromes caused by other conditions. In Khan’s study, 15 of 23 patients with moyamoya angiopathy had idiopathic MMD. Most European studies are focused on neurosurgical treatment and outcome parameters. In conclusion, only limited data exist about the presentation of MMD in American whites, but detailed demographic and clinical data about European white patients with MMD, to date, are almost nonexistent. Therefore, in this study, we aimed to clarify the demographic, clinical, and diagnostic and outcome features of MMD in European whites.

Materials and Methods
The design of this study was oriented on the protocols of the 2 relevant studies about MMD in the United States to enable a comparison.

Patient Selection
We identified all patients with angiographically proven idiopathic MMD evaluated at the neurological department at the Alfried Krupp Hospital.
Hospital, Essen, Germany, from 1996 through 2007. Inclusion criteria included unilateral or bilateral angiographic identification of severe stenosis or occlusion of the distal internal carotid, proximal middle cerebral, and anterior cerebral arteries associated with an abnormal network of collateral vessels. An exclusion criterion was the presence of secondary moyamoya phenomenon caused by atherosclerosis, meningitis, Down syndrome, systemic vasculitis, neurofibromatosis, or prior skull-base radiation therapy.

Retrospective Chart Review
Hospital charts, laboratory studies, duplex sonography, and special transcranial Doppler (TCD) sonography studies were reviewed as well as MRI, cerebral angiography, data on surgery, and histological reports. If necessary, records from outside hospitals were obtained and reviewed. Assessment was focused on demographic, clinical, and outcome features.

Clinical Follow-Up
In living patients diagnosed with MMD <1 year before data collection, the asked features were obtained from recent clinical visits. In living patients diagnosed ≥1 year before data collection, we invited the patients for an actual clinical follow-up visit. In some cases in which this was not possible, we tried to obtain follow-up data by a telephone interview, interview with actual treating doctors, and from outside hospital records. In patients whom we were not able to contact or from whom we obtained no actual data, features were determined from the last clinical visit.

Statistics and Data Analysis
Statistical comparisons were made using the Mann–Whitney U test (Wilcoxon test). Kaplan–Meier methods were used to estimate stroke risk. Statistical analysis was completed with SPSS version 13.0.

Results

Demographic Data
We identified 21 white patients with idiopathic MMD. Nonwhite patients and patients with secondary moyamoya phenomenon were excluded. Two were of Polish, one of Croatian, and 18 patients (85.7%) were of German family origin. Nineteen of the 21 patients (90.5%) presented bilateral vessel involvement. The female predominance was 4.25:1 (17.4 or 80.9% females). The mean age at onset of symptoms was 31 years ranging from 4 to 64 years (median age, 34 years). At onset of symptoms, one patient was 4 years old, 4 were 16 to 19 years, 4 were 21 to 29 years, 8 were 32 to 39 years, 3 were 40 to 45 years, and there was only one patient older than 45 years. The time from first symptom to correct diagnosis of MMD ranged from <1 month to 288 months. In 11 of 21 patients (52.4%), correct diagnosis was performed...
within 1 year (mean time to diagnosis, 44.81 months; median time to diagnosis, 11 months). The mean age at the time of diagnosis was 34.52 years; the median age was 38 years.

Familial Occurrence
In the majority of patients, the family illness history was unremarkable. In 2 female patients, the mother had an ischemic stroke; in one, this occurred at the age of 35 years. Two other patients reported cerebral ischemias at a young age in other family members. Family members’ cerebral angiography was not available for any of the patients, so it was not possible to diagnose a familiar occurrence of MMD in our cohort.

Baseline Stroke Risk Factors
Baseline cerebrovascular risk factors were documented in all patients. A total of 57.1% of patients (12 of 21) had no cerebrovascular risk factors. Six of 21 patients (28.6%) had only one cerebrovascular risk factor, which was mild smoking in 3 patients, cholesterol levels between 200 and 250 mg/dL in 2 patients, and mild adiposity in another patient.

Three of 21 patients (14%) had a combination of mild cerebrovascular risk factors at the time of diagnosis. Extracranial color-coded duplex sonography revealed minimal arteriosclerotic plaques only in 2 of 21 patients (9.52%), which was age-related in these patients. Risk factors were compared between surgically treated and nonsurgically treated patients; no significant differences (P=0.268) were observed. There was also no significant difference (P=0.234) between the rate of strokes between both groups with and without baseline cerebrovascular risk factors.

Disease Type
In our cohort, the initial symptom was a cerebral ischemic event in all patients. There was no patient with a hemorrhage at onset and there were no asymptomatic patients. Cerebral ischemic events included transient ischemic attacks (TIAs) as well as cerebral infarctions. Only one patient (4.8%) experienced subarachnoid hemorrhage 15 years after the first ischemic event. On cerebral angiography, 19 of 21 patients (90.5%) presented bilateral involvement.
Diagnostic Features
All patients underwent cerebral angiography and MRI with MR angiography. Almost all patients underwent extra- and intracranial color duplex sonography and special transcranial Doppler sonography studies. To exclude secondary moyamoya phenomenon due to autoimmune or infectious diseases, patients underwent extensive laboratory studies, including cerebrospinal fluid examinations.

Transcranial Doppler Detection of High-Intensity Transient Signals
In 14 of 21 patients (66.7%), detection of high-intensity transient signals (HITS) by TCD was available. Twenty-five TCD monitoring tests were analyzed. HITS detection by TCD was performed over 30 to 40 minutes with transcranial assessment of the middle cerebral artery. During TCD monitoring, HITS were detected in 3 patients (21.4%) with a total frequency of 5 (20%) in the 25 investigations. All patients with HITS showed hemodynamic compromise in functional regional cerebral blood flow studies. In these patients, HITS were recorded ipsilateral to the symptomatic hemisphere. All 3 patients with HITS were first diagnosed with bilateral MMD and showed 3 HITS over 30 minutes on one side. Detection of HITS was in the very beginning of the disease in all 3 patients with many transient and MR–tomographic-evident cerebral ischemic events. Two of these 3 patients were surgically treated; the control of HITS detection was normal. In one patient who was 29 years old when she experienced 3 left-sided ischemic strokes within only 1 week, TCD detection of HITS showed 3 HITS, 4 days later 3 HITS, 2 days later 2 HITS, and one day later no HITS.

Vasomotor Reactivity
With TCD, we determined vasomotor reactivity (VMR) as an indirect approach to measure cerebral autoregulation by the use of vasodilatory stimuli. In all but 2 (19 of 21 [90.5%]) patients, TCD was performed with a total of 33 examinations. Analyzing the TCD monitoring of these patients, we observed hemodynamic compromise with impaired or absent vasomotor reactivity in 25 of 36 hemispheres studied (69.5%).

Laboratory and Cerebrospinal Fluid Studies
In 13 of 21 patients (61.9%), liquor examinations were performed and were normal, including antibody studies (Borrelia and neurotropic viruses) and radial immunodifferentiation. In 15 of 21 patients (71.4%), serum blood studies included screening for autoimmune disease with antinuclear antibodies, antibodies to extractable nuclear antigens, antineutrophil cytoplasmic antibodies, and some more detailed laboratory studies. Only 3 of these 15 patients (20%) had borderline or moderate elevated antinuclear antibody levels, which were not specific for an autoimmune disease.

Treatments
Ten of the 21 patients (47.7%) were medically treated with antiaggregation drugs. Eleven patients (52.3%) underwent neurosurgical revascularization procedures, 5 of which were bilateral. None of the operation procedures were combined or single indirect bypass surgery (encephaloduroarteriosyn- giosis or encephalomyosynangiosis). All patients underwent superficial temporal artery to middle cerebral artery bypass surgery; in part of the patients, a modification with double superficial temporal artery to middle cerebral artery bypass surgery was performed. All surgically treated patients were affected with bilateral MMD; VMR in the affected hemisphere was clearly impaired or absent before the surgical procedure in all patients.

There was no significant difference between surgically treated and conservatively followed patients related to the number of strokes before diagnosis (P=0.539) or number of strokes after diagnosis (P=0.426) and number of all strokes (P=0.545). There was also no significant difference between both groups related to the number of strokes in the first 2 years after symptom onset (P=0.529) and the number of strokes thereafter (P=0.390).

Disease Progression and Follow-Up
The mean follow-up since diagnosis was 3.71 years (median, 3 years). All patients presented ischemic events. According to limitations of counting, the 21 patients experienced a total of 71 ischemic events (with a mean of events of 3.4 and a median of 3), including clinically diagnosed TIAs, clinically defined strokes, and MR–tomographic-evident cerebral ischemias. In the first 2 years after symptom onset, the patients experienced a total of 47 ischemic events (with a mean of 2.2 and a median of 3 events); later than 2 years after the first symptom, they experienced 24 ischemic events (with a mean of 1.1 and a median of 0 events). There was a significant difference between frequency of ischemic events in the first 2 years after symptom onset and thereafter (P=0.004).

The Kaplan–Meier estimate of recurrent stroke risk after the first ischemic event was 61.9% in the first year for all patients. The 5-year-Kaplan–Meier risk of recurrent stroke was 80.95% after the first ischemic event for all patients with a mean stroke-free survival time of 3.22 years (Figure 1). In medically treated patients, the Kaplan–Meier risk for recurrent stroke after the first ischemic event was approximately 80% in the first year. In surgically treated patients, the Kaplan–Meier risk for stroke after the first ischemic event was 45.45% in the first year (Figure 2). The Kaplan–Meier risk of recurrent stroke after angiographic diagnosis was 28.57% in the first 2 months with a 5-year-Kaplan–Meier risk of 37.5% for all patients (Figure 3). In medically treated patients, there was a subsequent stroke risk after angiographic diagnosis of 32.5% in the first 2.75 years; the surgically treated patients had a subsequent stroke risk after angiographic diagnosis of 45.45% in the first month. After surgery, the Kaplan–Meier risk of perioperative or subsequent stroke was 27.27% in the first month and was stable thereafter.

Functional Outcome
Actual follow-up information on disability and functional status was available for 15 of 19 surviving patients (78.9%). The outcome of the other 4 surviving patients was determined at the point of the final examination.

Two patients died (9.5%). One patient (4.8%) died of complications of MMD. This nonsurgically treated patient with bilateral MMD was documented to be Suzuki Grade 5.
seven years before she died from subarachnoidal hemorrhage 15 years after the first ischemic event. She had not taken any antiplatelet therapy during the last months before the bleeding. She was not followed up in our hospital but was referred to us for the first time to treat the bleeding, which unfortunately was not successful. The other patient died because of non-MMD-related complications. Some months after revascularizing surgery, this patient died of valproate acid-induced liver failure after receiving a combination with antibiotic drugs (Figure 4).

Thirteen patients (68.4%) had no disability (modified Rankin Scale of 0 and 1) and 6 of 19 surviving patients (31.6%) had mild or moderate disability but were able to walk (modified Rankin Scale of 2 or 3). None of the surviving subjects was severely disabled or unable to walk (modified Rankin Scale of 4 or 5).

All medically treated patients were not disabled at follow-up (modified Rankin Scale 0 and 1) and there was a trend to a better modified Rankin Scale in these patients compared with surgically treated patients but without statistical significance ($P=0.06$).

The functional outcome of patients was not significantly related to age ($P=0.291$), gender ($P=0.385$), number of strokes before diagnosis ($P=0.343$), number of all strokes ($P=0.068$), or vasomotor reactivity as measured with ultrasound methods ($P=0.436$).

**Histological Features**

In 7 of 11 surgically treated patients (63.6%), a biopsy was performed during the revascularizing procedure. In 6 of these patients, a cerebral blood vessel specimen was histologically analyzed; in 2, a perioperative brain biopsy was also analyzed. In both cases, the brain biopsy was evaluated to be normal in the pathological reports. Histological examination of 2 of the 6 vessel specimens revealed a thickened internal elastic lamina and intima, which are characteristic findings for MMD. In another histological report, fibrosis and dilatation of leptomeningeal vessels is described. The last 3 specimens were performed to exclude vasculitis. There were no signs of inflammation in these cases.

**Additional Symptoms and Diseases**

Amnestic data demonstrated that 9 of 21 patients (42.9%) had migraine-like headaches before and at the time of the first ischemic event of MMD. Two patients (9.5%) reported the triggering of transient or manifest ischemic events by hyperventilation. In 6 of 21 patients (28.6%), symptomatic epilepsy was diagnosed. The majority of the seizures was focal, so it was difficult to differentiate focal seizures from TIAs. In case of doubt, patients were treated with a probatory antiepileptic medication. Most of these patients with epilepsy were diagnosed after antiepileptic treatment resulting in an improved frequency of attacks. In one patient with bilateral MMD, we diagnosed the very rare limb-shaking TIAs induced by hyperventilation, which are a differential diagnosis to focal seizures. In 8 of 21 patients (38.1%), we diagnosed additional psychiatric or psychosomatic diseases like reactive depressive episodes and psychosomatic complaints. Half of these patients were surgically treated and all were bilaterally affected. There was no significant difference ($P=0.460$) between duration from first ischemic event to correct diagnosis of MMD in psychiatrically ill patients versus nonpsychiatrically ill patients.

**Discussion**

MMD remains rare outside the Far East, but the condition has been described on every continent and in all ethnic groups. Reviewing the literature, one realizes that the knowledge about MMD in non-Asians is minimal.

We present data from a cohort of 21 European white patients with idiopathic MMD with details about clinical manifestation, prognosis, and outcome.

Several differences between MMD in our European white cohort and Asian patients with MMD are notable, whereas there are similarities of our data with American patients with moyamoya disease.4,5

Because the diagnosis of MMD is based on its angiographic features, recognition is dependent on the performance of a digital subtraction angiography. The use of digital subtraction angiography in the evaluation of ischemic stroke of unknown etiology varies widely in practice. MMD may therefore be underrecognized as a cause of stroke.

MRI and magnetic resonance angiography have been acknowledged as noninvasive diagnostic modalities for MMD. Due to the guidelines for diagnosis of MMD modified and established by the Research Committee of the Ministry of Health and Welfare in Japan, conventional cerebral angiography is not mandatory if MRI and MR angiography clearly demonstrate all the following findings: (1) stenosis or occlusion at the terminal portion of the internal carotid artery and at the proximal portion of the anterior and middle cerebral arteries on MR angiography; (2) an abnormal vascular network in the basal ganglia in MR angiography; and (3) these findings are seen bilaterally.9

Most of our patients were young women. The age peak in childhood, typical for Asian patients, is not found in our study. We have to recognize the possibility of referral bias at our center. However, comparing our data with data from North American patients with MMD,4,5 it could be hypothesized that the difference in presentation of white and Asian patients may be related to the timing of onset of occlusive vasculopathy. All our patients presented with ischemic symptom onset, whereas most adults with Asian background present with hemorrhage. It is likely that ischemic events appear soon after the onset of the arterial occlusion or narrowing.4 In Asia, this most frequently occurs in childhood and the frequency of TIAs and cerebral infarctions is highest at that time.10 In accordance with American studies, we observed a higher risk for recurrent ischemic events in the first 2 years after symptom onset. This may reflect an improvement in collateral flow over time.

The increased risk for subarachnoidal hemorrhage in Asian adults may be the consequence of an extensive network of fragile moyamoya collaterals developing over decades since childhood. In our study, only one of the 21 patients experienced a subarachnoidal hemorrhage. We do not think that the predominance of ischemic disease is caused by a bias of data.
collection, but most likely by later manifestation of the disorder.

Asian epidemiological surveys have shown male-to-female predominance ranging from 1:1.8 in sporadic to 1:5 in familial cases of MMD.\(^1\) In the American ethnic heterogeneous analysis, there were female-to-male ratios of 2.5:1 and 1.8:1.\(^2\) In our European white cohort, the female predominance is more pronounced with 4.25:1. The results strongly suggest that female gender may be highly susceptible to the unknown factors causing MMD.

There was no evidence of familial MMD in our patients, but there were no angiographic data of family members available.

Analysis of baseline stroke risk factors demonstrates that most patients had no cerebrovascular risk factors and that minimal risk factors do not alter the stroke recurrence rate. Nevertheless, in clinical practice, patients with idiopathic MMD should be motivated to avoid smoking and cerebrovascular risk factors should be corrected.

In our study, a large quantity of special TCD examinations with detection of hemodynamic compromise by monitoring of VMR and detection of HITS is presented. HITS were detected in the very beginning of disease in all 3 patients with frequent MR–tomographically proven cerebral ischemic events. Despite our examinations, there are only limited data found in the literature about this topic.\(^3\)\(^,\)\(^4\) Horn et al\(^8\) reported HITS in 3 of 24 patients (12.5%) with a total frequency of 3 in the 45 hemispheres examined. The incidence of HITS in patients with MMD appears to be clearly lower than in patients with atherosclerotic or atherothrombotic arterial obstructions. In the beginning of the disease, embolic infarctions are sometimes seen. However, all patients with HITS also showed hemodynamic compromise in TCD examination of VMR. It could be argued that hypoperfusion could cause a reduced washout of emboli, in this way increasing the risk of clinically apparent embolism.\(^8\)\(^,\)\(^9\)

There are several paradigms to study cerebral autoregulation; measurement of VMR can be determined by the use of vasodilatory stimuli. VMR demonstrated hemodynamic compromises in 25 of 36 hemispheres studied at the point of the final examination. According to our experience, functional studies correlate with the angiographic stage of the disease.

In the only other relevant study, Horn observed hemodynamic compromise in 37 of 40 hemispheres studied and concluded that ischemia-related symptoms in “late-stage” MMD seem to be caused by hemodynamic compromise with watershed infarctions in the majority of patients.\(^8\) The main mechanism for the clinical symptoms observed is hemodynamic impairment; arterioarterial embolism is only evident in the minority of cases. The clinically relevant question is whether impaired or absent VMR or pathological single photon emission CT or xenon-CT justifies the decision for extracranial–intracranial bypass surgery.\(^1\)\(^3\) In MMD, the indication of surgical treatment is still a source of controversy. VMR testing should become an obligatory diagnostic tool in patients with MMD. VMR or autoregulatory investigations by single photon emission CT and xenon-CT could guide therapeutic decision to indicate extracranial–intracranial bypass, but good clinical outcome without ischemic events in many patients with impaired or absent VMR argues against this as a specific criterion.

Several limitations in the interpretation of the Kaplan–Meier estimates must be noted. The sample size of this study was small; the direct clinical follow-up was incomplete and the patient sample is heterogeneous with pediatric and adult cases. It is difficult to compare the Kaplan–Meier risk of medically treated and surgically treated patients because surgery was often performed after recurrent stroke in medically treated patients. Nevertheless, even being careful in interpreting the Kaplan–Meier risk values because of these limitations, it has to be stressed that dimensions of stroke risk are similar to American data reported by Hallemeyer et al.\(^4\)

The Kaplan–Meier risk for recurrent stroke after a first ischemic event is very high in our as well as in Hallemeyer’s cohort with a 5-year stroke risk of approximately 80% for all patients in our study and a 5-year stroke risk of 82% in medically treated bilaterally affected patients in Hallemeyer’s study.\(^4\) After angiographic diagnosis, the recurrent stroke risk is much smaller like after symptom onset in our study comparable to Hallemeyer’s results.\(^4\) In our surgically treated patients, the dimensions of stroke risk are small, similar to the American results,\(^4\) and are stable after a short time. Like in former studies, a substantial proportion of stroke risk in the surgical group is perioperative and postoperative and the data suggest that the late stroke risk is reduced.\(^5\)

It is interesting that we found no significant difference in the number of stroke experiences between surgically and medically treated patients even when regarding numbers of strokes before and after diagnosis and in the first 2 years and thereafter. However, there is a trend to better outcome in nonsurgically treated patients. In retrospect, we were not able to identify clear selection criteria for revascularization surgery; mostly, it was an individual decision. It could be hypothesized that not the number of strokes, but the severity of deficits after the stroke was a reason to indicate an operation. So the relatively poorer outcome in surgically treated patients is possibly not related to treatment complications but is biased by selection of different treatment options.

Reviewing retrospective charts combined with clinical follow-up information, one realizes how difficult it is to count the exact number of ischemic events even if documentation is well done. This is because many MR-evident ischemic lesions are clinically asymptomatic; clinical TIAs are associated with cerebral infarction in MRI and because of difficulties to differentiate TIAs from focal seizures. Despite these limitations in counting ischemic events, the significantly higher frequency of ischemic events in the first 2 years after symptom onset and thereafter argues for stabilization of the natural course of the disease.

In the literature, there are only rare data about histological features in MMD. In most cases, vascular structural changes were detected using postmortem specimens. In 2007, Takagi et al investigated 35 specimens of middle cerebral arteries from 25 Japanese patients undergoing surgical treatment of MMD.\(^1\) In our cohort, 6 vessel specimens were analyzed and 2 revealed histological features as described by Takagi et al. We suggest that analysis of a small vessel specimen should be obligatory in patients undergoing bypass procedures not only
for differential diagnostic reflections, but also to elevate our knowledge about this disease.

Reviewing additional clinical features, it is elucidating that 42.9% of the patients had migraine-like headache before and at the time of the first ischemic event of MMD. Several authors postulate that the pathophysiological mechanism of migraine-like headache in MMD could result in borderline perfusion in susceptible patients. It should be stressed that in young patients with stroke with atypical migraine-like headache, a detailed investigation should be kept in mind to detect an underlying vascular disease like MMD.

In 9.5% of our cohort, hypercapnia triggered transient or manifest ischemic events. Both patients showed hemodynamic compromise with impaired vasomotor reactivity. Kubawbara et al concluded that in adults as well as in children, cerebral hemodynamic reserve capacity decreases in response to hypercapnia. In Asian cohorts, ischemic events in children are often associated with hyperventilation. In MMD, it is sometimes difficult to differentiate between a clinical suspicion of focal epilepsy and TIA. Both may be triggered by hyperventilation. In one of our patients with MMD who also had focal seizures, ischemia presented with limb-shaking TIAs. In the literature, we found only one case report about limb-shaking TIAs in MMD; nevertheless, it is important to recognize and differentiate this condition from focal motor seizures in MMD. Limb-shaking TIAs are associated with severe stenosis or occlusion of the carotid artery. Orthostatic position change, hypotension, and hyperventilation have been reported to trigger these involuntary movements. In our cohort, in 6 of the 21 patients, symptomatic epilepsy was diagnosed. In case of doubt, a probatory antiepileptic medication should be initiated before a decision is made about surgical revascularization. There was a substantial number of patients with MMD with additional psychiatric or psychosomatic disease. It is important to differentiate dissociative symptoms from epileptic or ischemic events, which are referred to as an indication for bypass surgery.

Furthermore, we want to stress that the indication for revascularizing procedures should be built interdisciplinarily according to clinical features and not only on the basis of angiographic or other diagnostic features. Because the condition is rare and complications are frequent, MMD should be treated only in few specialized centers. A substantial number of European patients with MMD are treated in our hospital in Essen, Germany, by Schmiedek’s neurosurgical group in Mannheim, Germany, and by Yonekawa and Khan’s group in Zurich, Switzerland.

Comparing our results with other published studies, one realizes our results are consistent with American observations. White and Asian variants of MMD are different because most Asian adults with MMD present with hemorrhage, whereas ischemic events are typically observed in Asian children. It is likely that ischemic symptoms develop soon after the onset of the arterial narrowing or occlusion, which occurs in Asian MMD during childhood and later in whites. In the American series of Chui and Hallemeier, no patient experienced subsequent hemorrhage after initial presentation with an ischemic stroke, but in our cohort, one patient experienced lethal subarachnoidal hemorrhage. However, in the majority of our patients during the long follow-up, the disease became stable over time. This points out the question if there is a phase after which MMD may be considered quiescent or “burned out.” Comparing other clinical features in our white cohort with Asian studies, there is a similar frequency of additional symptoms like migraine-like headaches. Other differences between our cohort and Asian results like no evident familial presentation might be biased by a smaller cohort in contrast to greater Asian studies. In our opinion, most differences in presentation between Asian and white patients with MMD are related to the later timing of onset of this vaso-occlusive vasculopathy. We recognize the possibility of referral bias at our center, but other population-based surveys confirmed these differences of age at onset between Asian and non-Asian MMD.

This study expands our knowledge on MMD in Europe. White patients with MMD were at extremely high risk of future stroke; the risk appears to abate over time. The relationship among clinical course, angiographic, and other diagnostic features over time is not known. The role of surgical and conservative treatment in MMD needs further evaluation with larger cohorts with a focus on long-term clinical outcome.

Acknowledgments
We thank our colleagues from the neurological, neurosurgical, and neuroradiological departments of the Alfried Krupp Hospital (Essen, Germany) and colleagues from Prof Schmiedek’s neurosurgical group (Mannheim, Germany) for excellent cooperation in management of patients with moyamoya disease and syndrome. We especially thank L. Buentjen, MD (Essen, Germany), F. Diesner, MD (Essen, Germany), and R.R. Diehl, PhD (Essen, Germany). We thank C. Kraemer and M. Herold, MD, for important help and procreative discussions.

Disclosures
None.

References


Moyamoya Disease in Europeans
Markus Kraemer, Wilhelm Heienbrok and Peter Berlit

Stroke. 2008;39:3193-3200; originally published online September 11, 2008;
doi: 10.1161/STROKEAHA.107.513408
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/39/12/3193

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/