J Neurol (2010) 257:806–815
DOI 10.1007/s00415-009-5424-8

ORIGINAL COMMUNICATION

Neurocognitive dysfunction in adult moyamoya disease

Joanne R. Festa · Lauren R. Schwarz · Neil Pliskin · C. Munro Cullum · Laura Lacritz · Fady T. Charbel · Dana Mathews · Robert M. Starke · E. Sander Connolly · Randolph S. Marshall · Ronald M. Lazar

Received: 26 June 2009 / Revised: 24 November 2009 / Accepted: 9 December 2009 / Published online: 24 December 2009

Abstract We wanted to determine the neurocognitive profile of adult patients with moyamoya disease prior to neurosurgical intervention. The experience of three United States medical centers, Columbia University, University of Illinois at Chicago, and the University of Texas Southwestern Medical Center at Dallas, were combined. Clinical data from adult patients ($N = 29$) referred for neuropsychological evaluation from 1996 to 2008 were reviewed. Neurocognitive functioning was assessed using standardized neuropsychological tests and all data were converted to z-scores. Memory, attention, processing speed, verbal memory, visuo-spatial, language, and executive functions were examined. Cognitive dysfunction was defined as performance in two or more cognitive domains 1.5 standard deviations below age-corrected normative means OR one or more cognitive domains two standard deviations below age-corrected normative means. Manual strength and dexterity, as well as depressive symptoms, were also assessed. Two-thirds of patients demonstrated neurocognitive dysfunction. A large proportion of patients were found to have pronounced cognitive dysfunction (>2 SD below the mean) on tests of processing speed (29%), verbal memory (31%), verbal fluency (26%) and executive function (25%). Manual strength and dexterity were also affected in many patients, with impairment found in 36–58% of patients. Twenty-eight percent of patients reported moderate to severe depression, but depressive symptoms did not correlate with neurocognitive findings. A large proportion of adults with moyamoya disease demonstrate disruption of neurocognition in a broad range of functions, particularly those mediated by subcortical and frontal regions. The pattern of deficits suggests a mechanism of diffuse small vessel disease possibly caused by chronic hypoperfusion.

Keywords Moyamoya · Cognitive functioning · Neuropsychology

J. R. Festa (✉) · R. M. Starke · E. S. Connolly · R. S. Marshall · R. M. Lazar
College of Physicians and Surgeons,
Neurological Institute, Columbia University,
710 West 168th Street, Room 604, New York, NY 10032, USA
e-mail: jf2128@columbia.edu

L. R. Schwarz · N. Pliskin · F. T. Charbel
University of Illinois College of Medicine,
912 S. Wood Street, MC 913, Chicago, IL 60612, USA

C. M. Cullum · L. Lacritz · D. Mathews
University of Texas Southwestern Medical Center at Dallas,
5323 Harry Hines Blvd, Dallas, TX 75390-8846, USA

Introduction

Moyamoya disease (MMD) is a rare, chronic cerebrovascular occlusive condition of unknown etiology. The cerebrovascular hemodynamic impairment of MMD, produced by thickening and cellular proliferation in the vessel wall, most often leads to progressive, bilateral stenosis or occlusion of the intracranial internal carotid arteries together with an abnormal expansion of small vessels distal to the occlusion. Its characteristic appearance on cerebral angiogram, resembling a "puff of smoke," was first described by Takeuchi and Shimizu in 1957 [29]. The initial presentation of MMD can be transient ischemic attacks, cerebral infarction or intracranial hemorrhage in adults or children, although it has been reported that children and non-Asian adults more often present with transient motor disturbances [5, 7, 10, 12, 17, 23, 36, 37]. Among United States adult case series, the clinical features

variously include motor deficits, speech disturbances, headache, and seizure [5, 10, 23]. Surgical revascularization is the most frequent interventional procedure for MMD, but specific indications for treatment in adults are not well established [10, 21, 28].

Limited neurocognitive data from case and small-series investigations of pre-surgical adult patients with MMD have not shown consistent patterns, but rather demonstrate neuropsychological impairments in varying domains often consistent with stroke location. Specific impairments have been reported in processing speed [3, 24], visuo-spatial abilities [13, 24], verbal memory [13] and executive functions [15].

Although the initial neurological presentation and neuroradiological features of MMD have been described, the neuropsychological presentation of adult patients diagnosed with MMD is infrequently reported and has yet to be well characterized. Through the combined experience of three large university hospitals in the United States, we sought to examine the frequency and extent of cognitive impairment in MMD and describe more fully the neurocognitive profile of North American patients with adult-onset MMD.

Methods

Pre-surgical moyamoya adult patients over 18 years of age were referred for neuropsychological evaluation from 1996 to 2008 at three United States Medical Centers: Columbia University, University of Illinois at Chicago, and University of Texas Southwestern Medical Center at Dallas. The charts of patients diagnosed with MMD at the Universities of Illinois and Texas were retrospectively reviewed. Cases from Columbia University were enrolled in a prospective study of neurocognition in MMD. Cases were excluded if they had a history of developmental disorder or any neurological condition independently known to cause cognitive impairment.

Measures

Neurocognitive functioning was assessed using standard neuropsychological tests, with neurocognitive data converted to *z*-scores based on published, age-corrected normative means. These instruments were the same across all three centers with the exception of those evaluating verbal memory, which was assessed with either one of two tests, the Hopkins Verbal Learning Test or the California Verbal Learning Test, yielding similar indices: immediate recall, delayed recall, and recognition [4, 8]. Tests measured attention (Wechsler Adult Intelligence Test—III (WAIS-III) Digit Span and Arithmetic [31]), processing speed (WAIS-III Digit Symbol-Coding [31] and Trail Making Test Part A [26]), visuo-spatial skills (WAIS-III and Wechsler Abbreviated Intelligence Scale (WASI) Block Design [30, 31]), language (Boston Naming Test [14], Animal Fluency [18], and the Controlled Oral Word Association Test (COWAT) [2]), and executive functions (WAIS-III and WASI Similarities [30, 31], Trail Making Test Part B [26], and the Wisconsin Card Sorting Test (WCST) [11]). In addition, manual dexterity (Grooved Pegboard test [19]) and grip strength (Hand Dynomometer [27]) were evaluated. Depressive symptoms were assessed using either the Beck Depression Inventory-Second Edition or the Centers for Epidemiological Studies Depression scale [1, 25]. Cognitive domain scores were derived by averaging the *z*-scores within each domain for patients who received *all* of the domain measures: patients who did not receive all the domain measures were excluded from the analysis.

Cognitive dysfunction was defined by previously-established criterion based on performance deviation from the published normative means of each test in the six cognitive domains: Attention/Working Memory, Speed of Processing, Visual Construction, Memory, Language, and Executive Function [33]. Patients were categorized as having cognitive impairment [Domain Dysfunction (DD)] if $\geq$2 of 6 cognitive domains were >1.5 standard deviations (SD) below the normative mean OR if $\geq$1 of 6 cognitive domains were >2 SD below the normative mean. We also report the percent of patients with cognitive dysfunction below the >1.5 and >2 SD level for each test and cognitive domain.

Results

Of the 29 pre-surgical moyamoya adult patients, 14 (48%) were from Columbia University, 10 (35%) were from University of Illinois at Chicago and 5 (17%) were from the University of Texas Southwestern Medical Center at Dallas. MMD was angiographically verified in 28 cases (97%); the other case was diagnosed with MRA.

Average age at presentation was 40 years (39.9 $\pm$ 11.2; range 20–65). Seventy-nine percent were right handed, and gender was predominantly female (62%). Race/ethnicity was 59% Caucasian, 10% African-American, 10% Hispanic, and 21% Asian. Average education was 14 years (13.89 $\pm$ 2.74; range 8–20) and estimated intelligence, available for 86% of subjects (25/29), was in the average range (98.7 $\pm$ 17.2) [22, 32]. Initial clinical presentation leading to the neuropsychological evaluation was stroke in 22 patients (76%) of which 21 were ischemic; TIA in 5 patients (17%); and syncope in 2 patients (7%). Presenting symptoms were predominantly lateralized motor and

Table 1 Presenting symptoms

Symptom	*N*
Lateralized motor and sensory deficit	8
Lateralized sensory deficit	6
Lateralized motor deficit	4
Mental status change	4
Bilateral motor and sensory deficits	3
Headache	1
Lateralized motor deficit and mental slowing	1
Lateralized motor deficit and seizure	1
Lateralized sensory deficit and seizure	1

sensory (62%) and none presented with other localizing cognitive syndromes such as aphasia or apraxia (Table 1).

Means and SDs for results of the individual neuropsychological tests by domain are presented in Table 2. On individual tests, the poorest mean group performances were on delayed verbal memory (Delayed List Recall −1.3 SD below the mean), language (COWAT −1.2 SD below the mean), and executive function (Trail Making Part B −1.3 SD below the mean).

Of the 29 participants, 20 (69%) demonstrated neurocognitive dysfunction based on the DD criteria, with 62% of patients meeting both DD criteria. The number of patients with performance below the 1.5 and 2 SD levels is reported in Table 3. Functions for which patients most frequently had more pronounced impairment (below the 2 SD criterion) were processing speed (29% on Trail Making Part A), verbal memory (31% on Delayed List Recall), language (26% on COWAT) and executive function (25% on Trail Making Part B). Subjects' endorsements of depressive symptoms indicated that 36% had minimal symptoms, 36% had mild symptoms, 12% had moderate symptoms, and 16% reported severe symptoms. Depressive symptoms did not account for patients' cognitive dysfunction, since all correlations between depression scores and cognitive variables were nonsignificant.

The clinical information for each patient, including age, stroke history, medical comorbidities, medications, MRI and cerebral angiogram results, as well as test results reaching the impairment criteria of 1.5 and 2.0 SD below the normative mean, is presented in Table 4. The majority of patients, 83%, had a history of stroke, 17% (5/29) were taking antiepileptic drugs, 10% (3/29) were taking benzodiazapines, 31% had medical comorbidities that are risk factors for stroke (diabetes and hypertension), and 19 of the 28 patients (68%) had evidence of bilateral disease on cerebral imaging. As expected, a large proportion of the patients (86%) had a bilateral disease pattern on angiographic studies and 80% of those patients with a unilateral pattern did not demonstrate a lateralized pattern of deficits. Moreover, patients had a similar incidence of impairment regardless of stroke history: 84% of patients with and 75% of patients without stroke history had impairment on testing ($P = 0.553$).

Discussion

At initial clinical presentation and prior to any neurosurgical intervention, two-thirds (66%) of MMD patients had cognitive dysfunction. This is more than twice the rate

Table 2 Standardized results (*z*-scores) on neuropsychological measures and domains

Measure	Mean (SD)	Measure	Mean (SD)
Attention/working memory domain score	0.1 (1.3)	*Language domain score*	−0.8 (1.1)
WAIS-3 digit span [31]	0.2 (1.4)	Boston naming [14]	−0.7 (1.3)
WAIS-3 arithmetic [31]	0.0 (1.4)	COWAT [2]	−1.2 (1.3)
		Animal fluency [18]	−0.5 (1.2)
Speed of processing domain score	−0.8 (1.1)		
WAIS-3 digit symbol coding [31]	−0.5 (1.1)	*Executive functioning domain score*	−0.4 (0.8)
Trail making test part A [26]	−1.0 (1.6)	WAIS-3/WASI similarities [30, 31]	0.0 (1.0)
		Trail making test part B [26]	−1.3 (1.5)
Visual construction		WCST total errors [11]	−0.8 (1.1)
WAIS-3/WASI block design [30, 31]	−0.4 (1.3)	WCST perseverative errors [11]	−1.0 (0.9)
Memory domain score	−1.1 (1.4)	*Motor functioning domain score*	−1.6 (1.2)
Total list learning immediate recall [4, 8]	−1.0 (1.4)	Grooved pegboard dominant hand [19]	−1.4 (1.4)
Delayed list recall [4, 8]	−1.3 (1.8)	Grooved pegboard non-dominant hand [19]	−1.5 (1.6)
List recognition [4, 8]	−1.0 (2.2)	Grip strength dominant hand [27]	−2.0 (1.8)
		Grip strength non-dominant hand [27]	−1.8 (1.5)

Domain scores are the average of the domain test scores for patients who received *all* of the measures within that domain

Table 3 Percent of sample with cognitive dysfunction at the 1.5 and 2.0 SD levels

Measure	% (*N*) of sample 1.5 SD below the mean	% (*N*) of sample 2 SD below the mean
Attention/working memory domain score	21 (3/14)	0 (0/14)
WAIS-3 Digit Span[31]	19 (3/16)	6 (1/16)
WAIS-3 Arithmetic[31]	24 (4/17)	0
Speed of processing domain score	21 (4/19)	21 (4/19)
WAIS-3 digit symbol coding [31]	15 (3/20)	10 (2/20)
Trail making test part A [26]	36 (10/28)	29 (8/28)
Visual construction		
WAIS-3/WASI block design [30, 31]	29 (7/24)	4 (1/24)
Memory domain score	39 (10/26)	23 (6/26)
Total list learning immediate recall [4, 8]	31 (8/26)	23 (6/26)
Delayed list recall [4, 8]	46 (12/26)	31 (8/26)
List recognition [4, 8]	23 (6/26)	19 (5/26)
Language domain score	20 (5/24)	17 (4/24)
Boston naming [14]	32 (8/25)	24 (6/25)
COWAT [2]	41 (11/27)	26 (7/27)
Animal fluency [18]	16 (4/25)	12 (3/25)
Executive functioning domain score	19 (3/16)	0
WAIS-3/WASI similarities [30, 31]	9 (2/22)	0
Trail making test part B [26]	39 (11/28)	25 (7/28)
WCST Total Errors[11]	19 (4/21)	14 (3/21)
WCST perseverative errors [11]	24 (5/21)	14 (3/21)
Motor functioning domain score	61 (11/18)	44 (8/18)
Grooved pegboard dominant hand [19]	46 (10/22)	36 (8/22)
Grooved pegboard non-dominant hand [19]	50 (10/20)	45 (9/20)
Grip strength dominant hand [27]	58 (11/19)	53 (10/19)
Grip strength non-dominant hand [27]	53 (10/19)	42 (8/19)

Domain scores are the average of the domain for patients who received *all* of the measures within that domain

previously reported [15]. In our MMD patient sample, dysfunction was found on tests of memory, verbal fluency, processing speed, and executive functions, whereas attention and verbal reasoning were not affected. Our findings are consistent with other studies that demonstrate cognitive dysfunction in adult moyamoya patients but unique in showing that many adult patients with moyamoya have widespread neurocognitive dysfunction across two levels of impairment.

Other causes of cognitive and motor dysfunction such as presence of stroke, medication effects or medical co-morbidities were examined but did not account for the extent of impairment in the subjects. The concordance of cognitive and motor deficits with ischemic disease, for example, was variable: some patients had impairments with no focal ischemia while other patients had ischemic disease without deficits. Furthermore, the relatively young age of our patient sample suggests that atherosclerotic cerebrovascular disease was not a confounding etiology. In fact, only nine cases had atherosclerotic risk factors (hypertension or diabetes), making it more likely that the strokes were caused by hemodynamic failure from the moyamoya itself.

Medications, particularly anti-epileptic drugs (AEDs) and the benzodiazepine clonazepam could have contributed to dysfunction on testing. However, it is the long term use of multiple, older AEDs in epilepsy patients that have been shown to cause the greatest cognitive impairment [20]. All but one of those on AEDs were on AED monotherapy and only one was on a first-generation AED.

The pattern of deficits demonstrated in this sample from three university hospitals appears less attributable to focal stroke and more typical of diffuse small vessel disease possibly caused by chronic hypoperfusion. The global nature of cerebral dysfunction was further supported by the frequent bilateral abnormality in manual strength and dexterity not accounted for by frank ischemic events. The deficits in processing speed, verbal fluency, and executive functions are similar to those found in vascular cognitive

Table 4 Patient clinical information

Pt no	Age	Stroke history	Medical comorbidity	Medications	MRI results except where noted	Angiographic results	Deficits 1.5 SD below mean	Deficits 2 SD below mean
1	41	Yes	Mild TBI depression	Paroxetine	White matter strokes in R centrum semiovale, corona radiata, & R temporal lobe	Bilateral ICA stenosis no collaterals	None	None
2	20	Yes	Seizures	Gabapentin Divalproex	Focal atrophy over anterior interhemispheric fissure	Bilateral ICA stenosis with collaterals	COWAT	Delay recall; TMT A&B; animals; BNT; Pegs D&ND; Grip D&ND
3	25	No	Seizures	ASA & Dipyridamole Levetiracetam Warfarin	Ischemic changes in L frontoparietal region	Bilateral ICA stenosis with collaterals	Immediate recall; animals; BNT	Delay recall; TMT B; COWAT; Pegs D
4	29	Yes	HTN, DM HL	Warfarin Ramipril Nateglinide Metformin Insulin Simvastatin	Ischemia in R posterior frontoparietal region, old stroke in R centrum semiovale, corona radiata, posterior limb of internal capsule, cerebral peduncle, and pons	Bilateral ICA stenosis with collaterals	TMT A&B	Delay recall; Pegs D&ND
5	53	Yes	None	None	Bilateral inferior frontal and anterior temporal infarctions and white matter lesions	Bilateral ICA stenosis with evidence of MMD collaterals	Recognition Recall	Imm. and delay recall; TMT B; COWAT; BNT; WCST-P&E
6	34	Yes	Bipolar I APS Mitral Regurgitation	Divalproex Quetiapine ASA Clopidogre l Potassium-chloride Esomeprazole Atenolol Clonazepam Furosemide Albuterol HCTZ	Multiple bilateral white matter ischemic changes; R basal ganglia hemorrhagic infarction	Bilateral ICA stenosis with evidence of MMD collaterals	TMT A; WCST-E	Imm, delay and Recog. Recall; COWAT; BNT; Pegs D&ND
7	49	Yes	Back pain	HCTZ, ASA Morphine Polyethylene glycol Niacin Lansoprazole Clopidogrel Acetaminophen	Multiple high intensity signals in subcortical regions of L parietal lobe; old infarct in R basal ganglia	Bilateral ICA stenosis & distal portions of basilar artery, no collaterals	TMT B	TMT A

Table 4 continued

Pt no	Age	Stroke history	Medical comorbidity	Medications	MRI results except where noted	Angiographic results	Deficits 1.5 SD below mean	Deficits 2 SD below mean
8	49	No	HL, HTN Hepatitis stomach ulcer	Atorvastatin Valsartan Famotadine	No acute ischemia	Bilateral ICA stenosis with evidence of MMD collaterals	Delay recall TMT B; Blocks	Imm. recall; TMT A; WCST-P&E; Pegs ND; Grip D&ND
9	43	Yes	Migraine	None	Bilateral abnormal signal in both ACAs & small deep white matter hyperintensity in bilateral parietal region	Bilateral ICA stenosis with evidence of MMD collaterals	Pegs ND	WCST-P&E
10	54	Yes	Depression Diabetes	Venlafaxine Metformin Attenanol Atorvastatin HCTZ	Bilateral high anterior frontal infarction and white matter borderzone lesions	Bilateral ICA stenosis with expanded lenticulostriate vessels	Digits; Arithmetic; Blocks	Imm. recall; COWAT; Pegs D; Grip D
11	45	No	None	ASA	No lesions	Unilateral R MCA occlusion with expanded lenticulostriate vessels	Grip D&ND	Recog. recall
12	45	Yes	None	Midodrine Citalopram Testosterone Fludrocortisone	L insular gray matter and anterior bilateral basal ganglia infarcts, small bilateral frontal periventricular & subcortortical hyperintensities	Bilateral stenosis of MCAs & ACAs with expanded lenticulostriate vessels	Imm. recall; COWAT	Delay recall
13	33	Yes	Anxiety	Sertraline Desloratadine & Pseudoephedrine Zolpidem	L lenticulostriate hemorrhage, bilateral subcortical white matter & high convexity small infarcts	Bilateral proximal MCA & ACA stenosis with large lenticulostriate arteries typical for MMD.	COWAT	Pegs D&ND; Grip D&ND
14	24	Yes		Levetiracetam Sertraline Simvastatin ASA	R anterior frontal ACA territory & bilateral MCA-ACA border zone territories infarcts, R > L caudate nuclei infarcts	Bilateral disease R ICA occlusion, L MCA/ ACA occlusion with expanded lenticulostriate vessels	Blocks, TMT B	TMT A; Coding; Pegs D&ND
15	65	Yes	Neuropathy HTN	Amlopidine Carvedilol	No focal ischemia	Bilateral ICA & vertebrobasilar severe stenosis with expanded lenticulostriate vessels	Delay Recall	Recog. Recall; Pegs ND

Table 4 continued

Pt no	Age	Stroke history	Medical comorbidity	Medications	MRI results except where noted	Angiographic results	Deficits 1.5 SD below mean	Deficits 2 SD below mean
16	49	Yes	Afib depression	Esomeprazole Bupropion Clonazepam	L putamine & R basal ganglia hemorrhage	R MCA and bilateral PCA stenosis with expanded lenticulostriate vessels	Blocks	TMT A; Grip D&ND
17	43	No	HTN	Sertraline Atorvastatin Ibesartan ASA	Infarcts in centrum semiovale bilaterally, L frontal lobe cortical infarct, punctuate hemorrhages in L frontal & R parietal lobes	Bilateral ICA occlusions with expanded lenticulostriate vessels	None	WCST-P
18	34	Yes	Hepatitis B Migraine	No meds	L medial occipital, L lateral temporal, and bilateral frontal lobe infarcts	Bilateral ICA occlusions with expanded lenticulostriate vessels	Grip ND	Delay & recog. Recall; COWAT; Grip D
19	29	Yes	HTN	Gemfibrozil	Bilateral small white matter infarcts	Bilateral ICA occlusions with expanded lenticulostriate vessels	None	Pegs ND; Grip D&ND
20	45	Yes	None	Prednisone	High frontal, bilateral frontal and parietal white matter lesions	L MCA stenosis with expanded lenticulostriate vessels	Blocks; Pegs D&ND	TMT A&B; Grip D&ND
21	59	Yes	HTN	Enalapril Clonidine Nifedipine	R medial frontal infarct, multiple chronic microvascular ischemic changes & small caliber bilateral MCAs	Bilateral MCA stenoses with hypoplastic R ACA and occluded L ACA, with lenticulostriate and leptomeningeal collaterals	COWAT	None
22	30	No	Migraines, Hypothyroid	Verapamil Levothyroxine Venlafaxine Warfarin Amitriptyline Midrin®		Bilateral severe stenosis of carotid arteries with lenticulostriate collaterals	None	None
23	37	Yes	None	Amitriptyline ASA Esgic Plus®	CT: multiple ischemic lesions in frontal lobes, ischemic lesion in R caudate head	Left supraclinoid occlusion and poor collateral flow to L MCA territory	Similarities; arithmetic; blocks; digit span	Imm, delay & recog. recall, TMT A&B; animals; BTN; COWAT; Coding

Table 4 continued

Pt no	Age	Stroke history	Medical comorbidity	Medications	MRI results except where noted	Angiographic results	Deficits 1.5 SD below mean	Deficits 2 SD below mean
24	34	Yes	HTN Migraines	Phenytoin ASA	Infarct in L parietal & L posterior temporal lobe, further evolution of R frontal infarct, encephalomacic changes in R anteromedial frontal lobe, bilateral multiple deep white matter infarcts in the corona radiate & centrum semiovale	Bilateral occlusion of the supraclinoid ICAs	Similarities; Digit Span; Arithmetic; Coding	Delay Recall; TMT A&B; COWAT; BNT
25	36	Yes	HTN Migraine Cervical Spondylosis Obesity	Warfarin ASA Quinapril Metformin Amitriptyline Atorvastatin Midrin®	Multiple lesions in R MCA to ACA distribution	Bilateral stenosis of ICAs & stenosis or occlusion of ACAs	Arithmetic	None
26	41	Yes	Hypothyroid Suspected seizure	Levothyroxine ASA	Right frontal cortical and anterior parietal infarcts	Bilateral MCA stenosis	None	None
27	42	Yes	Fibroids	ASA	Deep white matter & subcortical white matter infarcts	Bilateral MCA & L ACA stenosis with expanded lenticulostriate vessels	None	Grip D&ND
28	47	Yes	DM, HTN	ASA Losartan Atorvostatin Clopidogrel Insulin glargine	Bilateral borderzone infarcts L > R	Bilateral MCA stenosis with expanded lenticulostriate vessels	Delay Recall	Imm. Recall; TMT B; BNT; Pegs D&ND Grip D&ND
29	21	Yes	Mild TBI	Fioricet® Alprazolam	Old lacunar infarct in R basal ganglia	R ICA stenosis, no collaterals	None	None

HTN hypertension, *DM* diabetes mellitus, *HL* hyperlipidemia, *APS* antiphospholipid antibody syndrome, *Afib* atrial fibrillation, *ASA* aspirin, *R* right, *L* left; *COWAT* Controlled Oral Word Association Test (Phonemic Fluency), *delay recall* delayed list recall; *TMT* Trail Making Tests (Parts A&B), *Animals* animal (semantic) fluency; *BNT* Boston Naming Test, *Pegs* Grooved Pegboard Test, *D* dominant, *ND* non-dominant, *grip* grip strength, *Imm. Recall* total list learning immediate recall, *WCST* Wisconsin Card Sorting Test (*E* errors; *P* perseverative errors), *blocks* WAIS-3 Block Design, *Digit Span* from WAIS-3; *Arithmetic* from WAIS-3; *Coding* WAIS-3 Digit Symbol-Coding, *Similarities* from WAIS-3

impairment, in which bihemispheral dysfunction is also expected [9]. Impairments in manual dexterity and cognitive flexibility have also been associated with greater subcortical white matter hyperintensities found in vascular cognitive cases [35]. Executive functions mediated by the frontal lobe, typically affected in vascular cognitive impairment, were also affected in this sample of moyamoya cases as well as in reports by others [3, 13, 15, 24].

A state of chronic hemodynamic compromise arising from long-term hypoperfusion, we believe, is the likely mechanism underlying the bilateral disease and deficits demonstrated in this moyamoya patient group. Cerebral hypoperfusion associated with cognitive dysfunction has been well-documented in MMD patients using perfusion-weighted MRI, with the most severe effects in the deep watershed territory of the white matter, in contrast to the relatively better perfusion in the occipital lobes, basal ganglia, brain stem and cerebellum [34]. Kim et al. [16] evaluated a group of adult, first-ever ischemic stroke moyamoya patients with single photon emission computed tomography (SPECT) and found that perfusion defects were larger than MRI ischemic lesions. Their pattern of abnormal cerebral blood flow in the anterior circulation suggested that the etiology of the ischemic lesions was predominantly hemodynamic compromise.

A link between chronic cerebral hypoperfusion and reversible neuronal dysfunction is supported by reports of revascularization resulting in increased cerebral blood flow and improvements in cognition [6]. In a case of moyamoya with preoperative bilateral hemispheral hypoperfusion on perfusion MR, extracranial–intracranial arterial bypass to the right cerebral hemisphere increased MR perfusion to normal levels in both hemispheres and resulted in improvements in right hemisphere neurocognitive functions [13].

There are several limitations to our study. First, our patient sample is subject to a referral bias: in two of the three institutions, the cases are representative of clinical referrals and do not reflect the neurocognitive profile of consecutive cases seen at the institution. Therefore, our reported sample may be biased toward patients with the greatest neurocognitive impairments. On the other hand, cognitive dysfunction may be generally under-represented in reports of moyamoya patients. In a recent report by Karzmark et al., an atypically conservative criterion was employed that required at least half of all cognitive tests to be 1 SD below the mean to meet the cut-off for mild impairment. Second, our data did not include perfusion studies that would have facilitated the assessment of cerebral hypoperfusion and its relationship to cognitive dysfunction in this sample. Third, our sample was not sufficiently powered to detect potential differences in race, gender or institution. Additional cases will be needed to examine the effects of epidemiological and clinical variables on cognition. Finally, there were some minor differences in the neurocognitive assessment measures used across the three medical centers, although attempts were made to equalize comparable results by evaluating outcomes by functional domains. Future multi-site studies should employ a battery to prospectively assess the broad range of functions potentially affected in moyamoya disease based on the assumed underlying mechanisms. Prospective evaluations should include serial structural and perfusion imaging. The inclusion of functional outcomes will provide validating information as to the impact of neurocognitive dysfunction as well as the impact of revascularization on daily functioning.

In conclusion, we found that prior to neurosurgical intervention, a large proportion of patients with moyamoya disease demonstrate disruption of neurocognition in a broad range of functions, particularly those functions mediated by subcortical and frontal systems. The lack of relationship between areas of ischemic lesions and neurocognitive dysfunction suggests the possibility of chronic hypoperfusion, rather than focal stroke, as a primary cause of the cognitive impairment. Our findings also emphasize the importance of performing neurocognitive evaluations to assess more comprehensively the full clinical impact of MMD; stroke-free moyamoya disease may not be a silent disorder when cognitive functioning is taken into consideration. Cognitive dysfunction may be an indication for earlier intervention with reperfusion procedures that can salvage ischemic neurons, restore cognition, and perhaps prevent new stroke onset.

Acknowledgment This work was supported in part by NIH:NCRR M01 RR 00645-27 Pilot Award, 2004.

Conflicts of interest statement There are no conflicts of interests to report.

References

1. Beck A, Steer R, Brown G (1996) Beck depression inventory, 2nd edn. The Psychological Corporation, San Antonio
2. Benton A, Hamsher K (1989) Multilingual aphasia examination. AJA Associates, Iowa City
3. Bornstein RA (1985) Neuropsychological performance in Moya Moya disease: a case study. Int J Neurosci 26:39–46
4. Brandt J, Benedict R (2001) Hopkins verbal learning test-revised. Psychological Assessment Resources, Odessa
5. Chiu D, Shedden P, Bratina P, Grotta JC (1998) Clinical features of moyamoya disease in the United States. Stroke 29:1347–1351
6. Chmayssani M, Festa JR, Marshall RS (2007) Chronic ischemia and neurocognition. Neuroimaging Clin N Am 17:313–324
7. Choi JU, Kim DS, Kim EY, Lee KC (1997) Natural history of moyamoya disease: comparison of activity of daily living in

surgery and non surgery groups. Clin Neurol Neurosurg 99(suppl 2):S11–S18
8. Delis D, Kramer J, Kaplan E, Ober B (1994) California verbal learning test, 2nd edn. Adult Version. The Pyschological Corporation, San Antonio
9. Hachinski V, Iadecola C, Petersen RC, Breteler MM, Nyenhuis DL, Black SE, Powers WJ, DeCarli C, Merino JG, Kalaria RN, Vinters HV, Holtzman DM, Rosenberg GA, Wallin A, Dichgans M, Marler JR, Leblanc GG (2006) National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards. Stroke 37:2220–2241 (see comment) [erratum appears in Stroke. 2007 Mar;38(3):1118 Note: Wallin, Anders (added)]
10. Hallemeier CL, Rich KM, Grubb RL Jr, Chicoine MR, Moran CJ, Cross DT III, Zipfel GJ, Dacey RG Jr, Derdeyn CP (2006) Clinical features and outcome in North American adults with moyamoya phenomenon. Stroke 37:1490–1496
11. Heaton R, Chelune G, Talley J, Kay G, Curtiss G (1993) Wisconsin card sorting test manual revised and expanded. Psychological Assessment Resources, Odessa
12. Ikezaki K, Han DH, Kawano T, Kinukawa N, Fukui M (1997) A clinical comparison of definite moyamoya disease between South Korea and Japan. Stroke 28:2513–2517
13. Jefferson AL, Glosser G, Detre JA, Sinson G, Liebeskind DS (2006) Neuropsychological and perfusion MR imaging correlates of revascularization in a case of moyamoya syndrome. AJNR Am J Neuroradiol 27:98–100
14. Kaplan E, Goodglass H, Weintraub S (1983) The Boston naming test, 2nd edn. Lea and Feinberg, Philadelphia
15. Karzmark P, Zeifert PD, Tan S, Dorfman LJ, Bell-Stephens TE, Steinberg GK (2008) Effect of moyamoya disease on neuropsychological functioning in adults. Neurosurgery 62:1048–1051 (discussion 1051–1042)
16. Kim JM, Lee SH, Roh JK (2009) Changing ischaemic lesion patterns in adult moyamoya disease. J Neurol Neurosurg Psychiatry 80:36–40
17. Kraemer M, Heienbrok W, Berlit P (2008) Moyamoya disease in Europeans. Stroke 39:3193–3200
18. Lezak M, Howieson D, Loring D, Hannay H, Fischer J (2004) Neuropsychological assessment, 4th edn. Oxford University Press, New York
19. Matthews C, Klove K (1964) Instruction manual for the adult neuropsychological test battery. University of Wisconsin Medical School, Madison
20. Mula M, Trimble MR, Mula M, Trimble MR (2009) Antiepileptic drug-induced cognitive adverse effects: potential mechanisms and contributing factors. CNS Drugs 23:121–137
21. Nakashima H, Meguro T, Kawada S, Hirotsune N, Ohmoto T (1997) Long-term results of surgically treated moyamoya disease. Clin Neurol Neurosurg 99(suppl 2):S156–S161
22. Nelson H, Willison J (1991) National adult reading test (NART): test manual, 2nd edn. NFER Nelson Windsor, UK
23. Numaguchi Y, Gonzalez CF, Davis PC, Monajati A, Afshani E, Chang J, Sutton CL, Lee RR, Shibata DK (1997) Moyamoya disease in the United States. Clin Neurol Neurosurg 99(suppl 2):S26–S30
24. Ogasawara K, Komoribayashi N, Kobayashi M, Fukuda T, Inoue T, Yamadate K, Ogawa A (2005) Neural damage caused by cerebral hyperperfusion after arterial bypass surgery in a patient with moyamoya disease: case report. Neurosurgery 56:E1380 (discussion E1380)
25. Radloff L (1977) The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Meas 1:385–401
26. Reitan R, Wolfson D (1985) The Halstead Reitan neuropsychological test battery. Neuropsychological Press, Tucson
27. Reitan R, Wolfson D (1993) The Halstead Reitan neuropsychological test battery: theory and clinical applications, 2nd edn. Neuropsychological Press, Tucson
28. Starke RM, Komotar RJ, Hickman SL, Paz YE, Pugliese AG, Otten ML, Garrett MC, Elkind MSV, Marshall RS, Festa JR, Meyers PM, Connolly ES (2009) Clinical features, surgical treatment, and long-term outcome of adult moyamoya patients. J Neurosurg 111:936–942
29. Takeuchi K, Shimizu K (1957) Hypogenesis of bilateral internal carotid arteries. No To Shinkei 9:37–43
30. Wechsler D (1990) Wechsler abbreviated intelligence scale. The Psychological Corporation, San Antonio
32. Wechsler D (1991) Wechsler test of adult reading. The Psychological Corporation, San Antonio
31. Wechsler D (1997) Wechsler adult intelligence scale, 3rd edn. The Psychological Corporation, San Antonio
33. White J, Hopkins RO, Glissmeyer EW, Kitterman N, Elliott CG (2006) Cognitive, emotional, and quality of life outcomes in patients with pulmonary arterial hypertension. Resp Res 7:55
34. Wityk RJ, Hillis A, Beauchamp N, Barker PB, Rigamonti D (2002) Perfusion-weighted magnetic resonance imaging in adult moyamoya syndrome: characteristic patterns and change after surgical intervention: case report. Neurosurgery 51:1499–1505 (discussion 1506)
35. Wright CB, Festa JR, Paik MC, Schmiedigen A, Brown TR, Yoshita M, DeCarli C, Sacco R, Stern Y (2008) White matter hyperintensities and subclinical infarction: associations with psychomotor speed and cognitive flexibility. Stroke 39:800–805
36. Yilmaz EY, Pritz MB, Bruno A, Lopez-Yunez A, Biller J (2001) Moyamoya: Indiana University Medical Center experience. Arch Neurol 58:1274–1278
37. Yonekawa Y, Ogata N, Kaku Y, Taub E, Imhof HG (1997) Moyamoya disease in Europe, past and present status. Clin Neurol Neurosurg 99(suppl 2):S58–S60