EFFECT OF MOYAMOYA DISEASE ON NEUROPSYCHOLOGICAL FUNCTIONING IN ADULTS

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OBJECTIVE: Moyamoya disease is a cerebrovascular disorder characterized by progressive occlusion of vessels comprising the circle of Willis, resulting in formation of collaterals that have a cloudy appearance on angiography. Neuropsychological research on the cognitive effects of the disorder in adults has been limited in scope and generalizability; only a few case studies have been published. The current study was intended to more comprehensively document the nature of cognitive impairment in moyamoya disease by assessing a large number of adult cases with a neuropsychological assessment test battery.

METHODS: Thirty-six adult patients with neurodiagnostically confirmed moyamoya disease were given presurgical neuropsychological assessments.

RESULTS: Mean group performances were within normal limits for all measures assessed. The highest rate of impairment was for measures of executive functioning. The lowest rates occurred with memory and perception measures. Cognitive impairment was present in 11 (31%) of the patients; it was judged to be moderate to severe in four patients (11%). Five patients reported a mild level of depression, and two patients reported a moderate level.

CONCLUSION: The present findings suggest that moyamoya disease diagnosed in adults can impair cognition but that the effect is not as severe as in pediatric cases. Executive functioning is most affected. Memory and, to a large extent, intellect are spared. The current pattern of results suggests brain region-behavior correlations that deserve further study.

KEY WORDS: Cerebrovascular disorders, Depression, Moyamoya disease, Neuropsychological tests

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Moyamoya disease is a rare cerebrovascular disorder of uncertain cause. It is characterized by progressive occlusion of the supraclinoid internal carotid artery and other vessels comprising the circle of Willis, resulting in formation of collaterals that have a cloudy appearance on angiography. Until recently, the disease was diagnosed primarily in Asia (4). It appears to have a bimodal age of onset, with diagnosis in the first or the third and fourth decades of life (26). Neuropsychological sequelae have been described and can be profound, at least with regard to intelligence in children (19, 25). However, research on cognitive effects of the disorder has been limited in scope and generalizability. Almost all research has included only intelligence testing. Most of the literature has originated in Japan and has primarily focused on pediatric cases. Many studies assess mental ability only after neurosurgical intervention.

Despite some early interest (11), there has been little neuropsychological research on moyamoya disease in adults. The adult literature is composed of five case studies (3, 11, 14, 18, 21). The results of presurgical neuropsychological testing in these cases indicate that impairment in intellect (18), speed of information processing (3), executive functioning (18), and visual spatial ability (11, 14, 21) can occur. In this small series of cases, the most consistent finding was relatively intact memory functioning (3, 18, 21). The only exception involved a case of right hemisphere infarction, resulting in impaired nonverbal memory (14).

Unfortunately, the characteristics of these case study patients make it difficult to deter-

mine the pattern of ability strengths and weaknesses in moyamoya disease, per se. Three of the patients (and questionably a fourth) had an infarction in the right hemisphere before neuropsychological testing (3, 11, 14, 21). The fifth patient had a diagnosis of schizophrenia and was actively psychotic when evaluated (18). The occurrence of a major cerebral infarction before neuropsychological testing raises a significant conceptual issue when attempting to understand the cognitive effects of moyamoya disease itself; the fundamental pathology may well be that of microvascular ischemia, but some patients do experience one or more major cerebral infarctions or hemorrhages. If major stroke is judged a separate entity, it is questionable whether the previous case studies should be considered as evidence for the effects of moyamoya disease on cognition. Previous case studies are also problematic because they varied substantially in the cognitive abilities assessed and in the tests used to evaluate these abilities. In some instances, a limited range of abilities was assessed.

The current study sought to more comprehensively document the nature of cognitive impairment in moyamoya disease by evaluating a large number of adult patients with a neuropsychological test battery.

PATIENTS AND METHODS

Patients

Between October 2004 and December 2006, 36 adult patients with neurodiagnostically confirmed moyamoya disease underwent presurgical neuropsychological assessment. A protocol reviewed and approved by the medical center's institutional review board was used. All subjects were proficient in English (Wechsler Adult Intelligence Scale III Vocabulary age scale score of ≥8). The average age was 36.6 years (standard deviation [SD] = 9.9). Mean education was 14.2 years (SD = 1.8 years). Twenty-four subjects were female, and 34 subjects were right-handed. Ethnicities were white (27), Asian (6), and African-American (3). Twenty-five subjects were in full-time paid employment. There were also five homemakers, five unemployed persons, and one retired person.

Neuropsychological Assessment

Intelligence was evaluated with the Wechsler Adult Intelligence Scale–Third Edition (27). Memory was assessed with the California Verbal Learning Test–II (6) and the Wechsler Memory Test–Revised Visual Reproduction subtest (28). A number of executive functioning tests were also administered to the subjects. These were the Delis-Kaplan Executive Function System Design Fluency Test (5), Letter and Category Fluency Tests (FAS and AN) (8), and the Trail Making Test Part B (24). Sensorimotor function was assessed with Grooved Pegboard (23) and the Tactile Form Recognition Test (24). Expressive language was measured with the Boston Naming Test (15), and speed of processing was measured with the Trail Making Test Part A (24). The Beck Depression Inventory (BDI)-II (1) was used as a self-report measure of depression.

The neuropsychological tests were administered to all subjects in accord with manual instructions. Subjects were evaluated in a single 3-hour session. Five subjects were not given the Tactile Form Recognition Test, and one subject did not take the BDI-II.

Data Analysis

Most raw cognitive test scores were converted to demographically adjusted (age, education, and sex) *t* scores using published normative data (10). These scores were then converted to *z* scores. Exceptions were the California Verbal Learning Test II, Wechsler Memory Test–Revised Visual Reproduction, and Delis-Kaplan Executive Function System Design Fluency Test. For these measures, age-adjusted *z* score equivalents were obtained following manual procedures. For all cognitive tests, *z* scores of 1 SD below the normative mean were considered to indicate impairment. For each test, the percentage of subjects with test performances more than 1 SD below the mean was calculated. Finally, the number of subjects with sufficiently poor overall performance to be characterized as cognitively impaired was calculated (9). This was defined as having, on average, at least half of a patient's test scores rated as at least mildly impaired (mild impairment was defined as 1–2 SDs below the mean). Moderate to severe impairment was defined as having, on average, at least half of a patient's scores at least moderately impaired (moderate impairment was defined as 2–3 SDs below the mean, and severe impairment was defined as ≥3 SDs below the mean).

A BDI-II score of 14 or greater was the criterion for the presence of depression (1). The number of subjects at each level of depression severity was tabulated.

RESULTS

The mean *z* scores for each clinical variable are presented in *Table 1*. None of the mean *z* scores were in the impaired range, indicating that, on average, performances were within normal limits for all measures given. The lowest scores were for Trail Making Test Forms A and B, FAS, AN, and Grooved Pegboard Test–Dominant and Nondominant Hands. The highest scores represented memory and vocabulary ability.

The percentage of subjects with scores in the impaired range for each measure is also shown in *Table 1*. The highest rates of impairment were for FAS, AN, Trail Making Test Form B (measures of executive functioning), Boston Naming Test, and Grooved Pegboard Test–Dominant and Nondominant Hands. The lowest rates occurred with memory measures, Tactile Finger Recognition Test, Delis-Kaplan Executive Function System Design Fluency Test, and Wechsler Adult Intelligence Scale III Vocabulary.

Cognitive impairment was present in 11 (31%) of the patients. This was judged to be moderate to severe in four patients (11%).

The mean score on the BDI-II was within normal limits (mean = 10.1, SD = 5.4). Only seven of the subjects obtained scores in the clinical range. Five of these subjects reported a mild level of depression, and two reported a moderate level.

DISCUSSION

This is the first study to evaluate the effect of moyamoya disease on cognition in a large series of adults. Previous research has been limited to several case studies. The present findings suggest that moyamoya disease diagnosed in adults has significant impact on cognition but that this effect is not severe or pervasive. On measures of intelligence and other cognitive abilities,

TABLE 1. Mean *z* scores and percentage of patients performing in the impaired range for each measure[a]

Test	Mean *z* score	Test impairment (%)
Intelligence (WAIS-III)		
Verbal IQ	–0.5	25
Performance IQ	–0.5	25
Full Scale IQ	–0.6	19
Vocabulary	–0.1	8
Similarities	–0.3	25
Arithmetic	–0.6	31
Digit Span	–0.5	33
Comprehension	–0.4	31
Picture Completion	–0.4	25
Digit Symbol	–0.5	36
Block Design	–0.4	28
Picture Arrangement	–0.4	25
Memory		
CVLT II Total Words Recalled	0.0	14
CVLT II Long Delay Free Recall	–0.4	19
WMS-R Visual Reproduction Immediate	0.5	0
WMS-R Visual Reproduction Delayed	0.4	0
Executive abilities		
Trail Making Test B	–0.8	42
Letter Fluency (FAS)	–0.9	47
Category Fluency (AN)	–0.9	44
D-KEFS DFT Total Attempted Designs	0.0	11
Sensorimotor functions		
Grooved Pegboard Dominant Hand	–0.8	42
Grooved Pegboard Nondominant Hand	–0.5	33
Tactile Form Recognition Right Hand[b]	0.1	6
Tactile Form Recognition Left Hand[b]	0.0	13
Speed of information processing		
Trail Making Test A	0.9	39
Language		
Boston Naming Test[c]	–0.6	40
Mood		
Beck Depression Inventory II[c]		20

[a] WAIS-III, Wechsler Adult Intelligence Scale–Third Edition; IQ, intelligence quotient; CVLT II, California Verbal Learning Test–Second Edition; WMS-R, Wechsler Memory Scale–Revised; D-KEFS DFT, Delis-Kaplan Executive Function System Design Fluency Test.
[b] n = 31 for Tactile Form Recognition Test
[c] n = 35 for Boston Naming Test and Beck Depression Inventory II.

mean performance was within normal limits on all tests given. Mean Full Scale Intelligence Quotient (IQ) was 95. This is in contrast with the usual finding in pediatric moyamoya disease, in which significant loss of intellectual capacity is common. In a group of 104 pediatric cases, 38% had a Full Scale IQ or equivalent of less than 80 (12, 13, 19, 22, 25). In contrast, 11% of the patients in the current study had a Full Scale IQ of less than 80, suggesting that with diagnosis in adulthood the effects of the disorder are generally milder than with early onset. This is reflected in the proportion (84%) of the current sample who were gainfully employed at the time of assessment. The finding of relative sparing of cognition in adult moyamoya disease has not been documented previously. The cause of this sparing is not known, but it may be related to a differential effect of the disease on the developing and mature nervous systems.

In general, intellectual functioning is less affected by neurological disorders than other aspects of cognition, such as memory and mental flexibility (16). For this reason, understanding the effects of a neurological disorder on mental functioning requires comprehensive neuropsychological evaluation. Such an evaluation in the current study indicates that moyamoya disease, although not severe or generalized in its effects, does result in cognitive impairment in adults. This is most apparent in executive functioning. Approximately half of the patients in the current study had impairment in executive abilities, such as initiation and mental set-shifting efficiency. In the three previous case studies in which executive functioning was measured (3, 14, 18), impairment was found on some measures but not others. The consistent impairment of executive abilities in the current study raises the possibility that adult moyamoya disease affects frontal lobe function.

Deterioration in memory capacity has been identified as one of the most frequent effects of damage to the brain in general (17). This highlights the striking lack of memory impairment in the present study. This sparing is consistent with the results from previous research on moyamoya disease, which rarely indicates memory impairment (3, 18, 21). Together, these results suggest that the medial temporal area of the brain and associated structures subserving memory function tend to be spared by moyamoya neuropathology. This may reflect the geographic distribution of the vascular pathology underlying moyamoya disease.

The prevalence of depression after the onset of discrete neurological events such as stroke or head injury is high: 20 to 40% (20). However, moyamoya disease is usually not a discrete event, but rather a subacute or chronic disorder with gradual or stepwise progression. Therefore, a reasonable analog group might be patients with epilepsy who are awaiting surgical intervention. Moderate to severe depression on the BDI has been reported in 22% of such a group (7). The low rate (5%) of substantial depression in our patients with moyamoya disease was unexpected. A number of differences between the two groups might account for the different rates of depression. The patients with moyamoya disease seemed to perceive the disease as having modest impact on their activities and abilities, and there was a comparatively short latency between diagnosis and surgical intervention (median, 3 mo). In contrast, patients with epilepsy typically have substantial psychosocial and activities of daily living losses (e.g., loss of driving privilege). They also have a lengthy experience of failed medication trials before surgical treatment is considered, with an average latency from onset to surgical evaluation of 9 years in one study (2). The perceived lack of impact of moyamoya disorder on quality of life will be addressed in a future study.

The incidence of discrete cerebrovascular events in the current sample is unknown. Thus, the proportion of neuropsychological impairment that can be attributed to moyamoya disease itself, as opposed to secondary ischemia or hemorrhage, is also unknown. In previous adult case studies, some form of stroke had occurred in most of the patients before assessment, and the cognitive impairment found in these studies may have resulted from stroke, rather than moyamoya disease. Separation of these factors would be an important goal for future studies and is anticipated in a future article by our group.

CONCLUSION

The current study is the first systematic and comprehensive examination of the cognitive effects of moyamoya disease in adults. Pediatric research suggests substantial and pervasive impairment in mental functioning. In contrast, the current results indicate clear but selective impact on cognition in adults, with many ability domains spared and several clearly affected. The pattern of results also suggests brain region-behavior correlations that deserve further exploration.

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COMMENTS

Karzmark et al. present their results on presurgical neuropsychological assessments on 36 adult patients with radiographically confirmed moyamoya disease. They demonstrate a deficit in nearly one-third of patients with executive functioning. Interestingly, unlike pediatric patients who show significant deficits in memory, no such deficits in adults were observed. This is an important first study; however, there are several major limitations including small numbers of patients studied. Another major weakness is the conclusion that the deficits observed are attributable to the moyamoya disease itself, and not to strokes. Without a correlation with imaging studies, this conclusion cannot be reached. These weaknesses are not noted adequately in the Discussion. Further studies with prospective follow-ups and those aimed at assessing the effects of surgery on cognitive functioning will be important.

Murat Gunel
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In this report, Karzmark et al. sought to comprehensively document the nature of cognitive impairment in adult moyamoya disease using neuropsychological tests. This is the first report to evaluate the cognitive function of moyamoya disease in a large series of adult patients. In pediatric patients, serious cognitive impairment is the most serious problem. But the present study showed that such serious cognitive dysfunction is rarely found in adult patients. Almost half of the patients in the current study had impairment in executive abilities such as initiation and mental set shifting efficiency. On the contrary, memory impairment was seldom observed. These results indicate that adult moyamoya disease affects frontal lobe function but not the medial tem-

poral region. As noted in the text, it is difficult to know what produces the results in the neuropsychological tests. The result obtained in this study needs to be compared with that obtained using patients with the usual cerebral infarction and intracerebral hemorrhage. We hope that the authors will analyze the result in more detail on the basis of neuroradiological and clinical findings in the future. However, it is an important article for clarifying the pathophysiology of adult moyamoya disease.

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On the basis of their extensive experience in the management of moyamoya disease, these authors from Stanford University have sought to more comprehensively document the nature of cognitive impairment in patients with this disease. To achieve their goal, the authors evaluated 36 patients with neurodiagnostically confirmed moyamoya disease using a battery of validated neuropsychological tests. Cognitive abilities tested included intelligence, memory, executive functioning, sensorimotor function, expressive language, and depression.

Interestingly, the mean group performances were within normal performances for all measures given. The highest scores represented memory and vocabulary ability, whereas the highest rate of impairment was seen in executive functioning. Compared with similar studies performed in the pediatric population suffering from moyamoya disease, cognitive impairment was less frequent and less profound.

As pointed out by the authors, these findings may lend insight into the brain regions most commonly impaired by moyamoya disease. The study also establishes a baseline understanding of the effects of the disease for purposes of comparing outcomes with various therapeutic interventions.

The primary weakness of this study is the unknown incidence of preexisting infarctions that may have contaminated the data to an unknown degree. Most patients referred for neurosurgical management of moyamoya disease have experienced some symptoms that led to the diagnosis. The cognitive impairment owing to the presenting stroke, as opposed to that attributable to moyamoya disease itself, is an important objective for future studies.

The authors have raised the bar for outcome assessment of patients with neurological diseases. By using validated neuropsychological tests, the deleterious effects of neurological disease and results of management can be assessed with more objectivity than the highly subjective outcomes often found in the literature.

Daniel L. Barrow
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Karzmark et al. investigated the level of cognitive impairment in moyamoya disease by assessing 36 adults patients preoperatively using a neuropsychological assessment test battery. Results demonstrated that although mean group performances were within normal limits, the highest rate of impairment was for measures of executive functioning, whereas the lowest rates occurred with memory and perception measures. Of note, cognitive impairment was evident in nearly one-third of patients, being moderate to severe in four individuals. The authors concluded that adult moyamoya disease can impair cognition and more specifically executive functioning but to a lesser extent than in pediatric patients.

This investigation elucidates the subtle changes in cerebral function that may occur secondary to altered cerebral circulation in moyamoya syndrome. In future studies preoperative and postoperative neuropsychometric tests should be compared to detect potential surgical benefit or morbidity. It is hoped that by identifying factors that predict postoperative neurocognitive dysfunction in certain individuals, patient selection for bypass surgery may be further delineated.

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The authors presented the first systematic and comprehensive examination of the cognitive effects of moyamoya disease in adults. They evaluated 36 adult patients with neurodiagnostically confirmed moyamoya disease using a presurgical neuropsychological test battery that assessed intelligence, memory, executive functioning, sensorimotor function, expressive language, speed of processing, and depressive symptoms. Cognitive impairment was present in 31% of patients. The highest rate of impairment was for measures of executive functioning, and the lowest rates occurred with memory and perception measures. This article shows that, although not severe or generalized in its effects, moyamoya disease does result in cognitive impairment in adults and that this impairment is generally milder than that in pediatric moyamoya disease.

As mentioned by the authors, the proportion of neuropsychological impairment that can be attributed to moyamoya disease itself, as opposed to secondary ischemia or hemorrhage, is unknown. It would be very interesting to differentiate between primary and secondary damage in moyamoya disease. Furthermore, it would be extremely useful to evaluate the impact of surgical treatment on reducing primary and/or secondary cognitive impairment in moyamoya disease.

Interestingly, it seems that there is an anatomical explanation for the pattern of results of this study. The posterior cerebral artery provides the main arterial supply to the hippocampal formation and fornix and the posterior communicating artery usually irrigates the mammillary bodies. Thus, selective sparing of these branches of the posterior circulation may explain the striking lack of memory impairment showed in the present study. Future studies from the Stanford group will surely increase current knowledge of moyamoya disease.

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