

Predictors of Cognitive Dysfunction After Subarachnoid Hemorrhage

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Background—Cognitive dysfunction is a common and disabling sequela of subarachnoid hemorrhage (SAH). Although several clinical and radiographic findings have been implicated in the pathogenesis of cognitive dysfunction after SAH, few prospective studies have comprehensively and simultaneously evaluated these risk factors.

Methods—Between July 1996 and March 2000, we prospectively evaluated 113 of 248 consecutively admitted nontraumatic SAH patients alive at 3 months with a comprehensive neuropsychological evaluation. Summary scores for 8 cognitive domains were calculated to express test performance relative to the entire study population. Clinical and radiographic variables associated with domain-specific cognitive dysfunction were identified with forward stepwise multiple regression, with control for the influence of demographic factors.

Results—The study participants were younger ($P=0.005$), less often white ($P=0.006$), and had better 3-month modified Rankin scores ($P=0.001$) than those who did not undergo neuropsychological testing. The proportion of subjects who scored in the impaired range (>2 SD below the normative mean) on each neuropsychological test ranged from 10% to 50%. Predictors of cognitive dysfunction in 2 or more domains in the multivariate analysis included global cerebral edema (4 domains), left-sided infarction (3 domains), and lack of a posterior circulation aneurysm (2 domains). Other variables consistently associated with cognitive dysfunction in the univariate analysis included admission Hunt-Hess grade >2 and thick SAH in the anterior interhemispheric and sylvian fissures.

Conclusions—Global cerebral edema and left-sided infarction are important risk factors for cognitive dysfunction after SAH. Treatment strategies aimed at reducing neurological injury related to generalized brain swelling, infarction, and clot-related hemotoxicity hold the best promise for improving cognitive outcomes after SAH. (*Stroke*. 2002;33:200-209.)

Key Words: cerebral aneurysm ■ cerebral arteriovenous malformations ■ stroke ■ subarachnoid hemorrhage

Subarachnoid hemorrhage (SAH) is a devastating illness with a 30-day mortality rate of 30% to 40%.¹ Although most survivors are free of physical handicap, approximately 50% remain permanently disabled because of cognitive dysfunction.¹ SAH patients may experience deficits in verbal and nonverbal memory, psychomotor speed, executive function, visual-spatial function, and other cognitive domains.^{2,3} The fact that 50% of patients who were previously employed do not return to the same level of work after SAH attests to the devastating nature of these deficits.⁴

Although it is an important clinical problem, relatively little is known about the precise cause of cognitive impairment after SAH.² Current understanding of the pathogenesis of cognitive impairment after SAH is particularly hindered by the diversity of neurological insults that may occur. In the prevailing view, the typical pattern of mild-to-moderate dysfunction across multiple cognitive domains has been

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thought to reflect diffuse injury caused by ictal intracranial circulatory arrest^{5,6} and exposure of the brain to subarachnoid blood.² Other studies of cognitive outcome after SAH have identified intracerebral and intraventricular hemorrhage (ICH and IVH),⁵ hydrocephalus,⁵ delayed cerebral ischemia (DCI) or infarction,^{5,7,8} and aneurysm location^{8,9} as risk factors for domain-specific cognitive dysfunction.³ The relative importance of these different types of injury is unknown, however, and other possible mechanisms of injury, such as cerebral edema, remain unexplored. Further complicating the assessment of cognitive outcomes after SAH is the profound effect that patient-specific demographic characteristics, such as age and education, have on neuropsychological test performance¹⁰ and the course of recovery after SAH.⁵

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Identification of specific events and pathophysiological processes that cause cognitive dysfunction after SAH may lead to the development of targeted interventions that may improve outcome. The purpose of this study was to evaluate the relative impact of a diversity of distinct pathophysiological processes on cognitive outcome after SAH while controlling for demographic variables. Specifically, we sought to identify particular clinical and radiographic risk factors during the acute phase of SAH that relate to 3-month global and domain-specific cognitive dysfunction.

Subjects and Methods

Patient Population

Three hundred twenty-six SAH patients admitted consecutively to our Neurological Intensive Care Unit (NICU) between July 1996 and March 2000 were prospectively enrolled in the Columbia University SAH Outcomes Project. The study was approved by the hospital Institutional Review Board, and in all cases written informed consent was obtained from the patient or a surrogate.

The diagnosis of SAH was established by computed tomography (CT scan) or xanthochromia of the cerebrospinal fluid if the CT was negative. Exclusion criteria included SAH from trauma or rupture of an arteriovenous malformation, admission >14 days after onset (68% were admitted within 1 day of index bleed and 95% within 7 days), and age <18 years.

Clinical Management

Ruptured aneurysms were treated with surgical clipping or coil embolization as soon as possible, with the exception of some Hunt-Hess grade V patients whose extremely poor condition precluded immediate treatment. All patients received oral nimodipine. While patients were in the NICU, transcranial Doppler (TCD) sonography was performed daily or every other day. All patients with signs of elevated intracranial pressure and hydrocephalus were treated with external ventricular drainage (EVD). Patients were given 0.9% saline and supplemental 5% albumin solution to maintain central venous pressure >8 mm Hg, and those with clinical deterioration from DCI were treated with hypertensive hypervolemic therapy (HHT) with vasopressors to maintain systolic blood pressure >200 mm Hg. When significant clinical symptoms persisted despite HHT, angiography with balloon angioplasty of vasospastic vessels was performed if feasible.

Clinical and Radiological Assessment

Basic demographic data (age, sex, race/ethnicity, fluency in English, education level), social and past medical history, and clinical features at onset were obtained by review of the medical record and interview of the patient and family shortly after admission. Cognitive status on day 14 (or discharge if earlier) was evaluated with the Telephone Interview of Cognitive Status (TICS).¹¹ A complete review of the entire hospital course was conducted at the time of discharge by a study neurologist to document important procedures, events, and complications.

Each patient's admission and discharge CT scan, as well as those with significant interval changes during hospitalization, were independently evaluated by a study neurologist for the amount and location of SAH, IVH, and ICH; the severity of hydrocephalus; and the presence of acute infarction or cerebral edema. The amount of SAH in 10 individual cisterns or fissures on the admission CT scan (and after an episode of rebleeding) was quantified according to the method of Hijdra et al.¹² Hydrocephalus was evaluated by the bicaudate index (considered present when it exceeded the upper limit of normal per decile of age) and the mean temporal horn diameter.¹³ "Treated hydrocephalus" was defined by treatment with lumbar puncture or drainage, EVD, or ventriculoperitoneal shunting. Cerebral edema was classified as global or focal, with focal edema classified as being related to infarction, hemorrhage, retraction

injury, EVD placement, or other. Global edema was diagnosed when effacement of the hemispheric sulci or basal cisterns was present, in combination with disruption of the hemispheric gray-white matter junction due to either blurring or diffuse "finger-like" extension of the normal demarcation between gray and white matter.

DCI was defined as otherwise unexplained (1) clinical deterioration (ie, a new focal deficit, decrease in level of consciousness, or both) and/or (2) a new infarct on CT that was not visible on the admission or immediate postoperative scan. Other potential causes of clinical deterioration, such as hydrocephalus, rebleeding, or seizures, were rigorously excluded. Patients were classified as having TCD evidence of vasospasm if the mean velocity of any vessel exceeded 140 cm/s.¹⁴

Predictor Variables

Clinical and radiological predictor variables were grouped into 6 categories, as follows: (1) clinical condition: admission and worst Hunt-Hess scale score,¹⁵ admission Glasgow Coma Scale (GCS) score,¹⁶ admission Neurological Institute of Health Stroke Scale (NIHSS) score,¹⁷ admission Acute Physiology and Chronic Health Evaluation-2 (APACHE-2) score¹⁸ (a physiological subscore was calculated by subtracting the GCS score, age, and chronic health elements from the total score); (2) hemorrhage: admission Hijdra SAH sum score,¹² complete filling of any of 10 cisterns and fissures, any IVH, any ICH, right or left ICH; (3) hydrocephalus: bicaudate index,¹³ mean temporal horn diameter, EVD, ventriculoperitoneal shunt, treated hydrocephalus; (4) ischemia: right-sided, left-sided, or any acute infarction; DCI; TCD vasospasm; (5) edema: global, focal, or any cerebral edema; and (6) aneurysm location: anterior communicating, left-sided or right-sided anterior circulation, posterior circulation, nonaneurysmal.

Three-Month Follow-Up Assessment

Three months after the onset of SAH, each subject and their nearest relative or spouse were asked to complete a 45-minute in-person or telephone basic outcomes assessment in their native language (English or Spanish). This evaluation included a structured interview assessing interim medical and social history, medications, rehabilitation, and work status. Global outcome was assessed with modified Rankin Scale.¹⁹ Other instruments used to assess global outcome, disability, quality of life, cognitive function, depression, and anxiety are available from the authors by request.

Subjects were also asked to complete a 3-hour battery of neuropsychological tests whenever possible (a complete list of the test battery and references are available from the authors by request). Raw test scores with significantly skewed distributions were transformed by square root, logarithmic, or inverse transformations as necessary to satisfy the assumption of normality. Data transformation of this type improves the ability of parametric statistical tests to identify trends while maintaining relative relationships between scores.²⁰ By use of these data, summary scores for 8 cognitive domains were created for each patient by selection of 2 or 3 primary scores from related neuropsychological tests that tap similar cognitive functions, chosen on the basis of face validity (Table 1). These scores were converted to sample Z scores (raw score—sample mean/sample SD) and averaged to derive a summary score for each domain. We used the Kolmogorov-Smirnov test to confirm normality of all domain scores.²⁰

For descriptive purposes, we also converted raw test scores to norm-adjusted Z scores based on published normative data (when available) and calculated the proportion of subjects who scored in the clinically impaired range on each test (≥ 2 SD below the normative sample mean). We used sample rather than normative Z scores for the statistical analysis because in most cases significant associations with demographic factors persisted even after correction using published normative data.

Statistical Analysis

All data analyses were performed with commercially available statistical software (SPSS version 9.0, SPSS Inc). We evaluated

TABLE 1. Neuropsychological Test Performance

Cognitive Domain	Tests	Test Range (Poor–Good)	Sample Range	Mean Raw Score	Mean Z Score*	Percent Impaired
Global mental status	TICS‡ (cut point≤30)	0–51	14–46	32.9	NA	36
	Katzman OMC‡ (cut point≥6)	28–0	28–0	4.4	NA	26
Visual memory	WMS-R Visual Reproduction II§	0–41	0–41	19.8	−0.7±1.4	22
	RCFT–delayed recall§	0–36	0–35	14.5	−1.4±1.3	31
	WAIS-R Digit Symbol recall	0–9	0–9	5.1	NA	...
Verbal memory†	CVLT Trials 1–5§	0–80	10–68	43.6	−1.5±1.3	48
	CVLT Short Delay Free Recall§	0–16	0–16	8.0	−1.6±1.6	50
	CVLT Long Delay Free Recall§	0–16	0–16	8.3	−1.7±1.6	48
Reaction time (RT)	Cal-CAP–Simple RT (ms)‡§	5000–0	1184–230	412	−0.3±1.2	11
	Cal-CAP–Choice RT (ms)‡§	870–0	805–335	490	−1.1±1.5	33
	Cal-CAP–Sequence 1 (ms)§	870–0	856–343	644	−1.0±1.3	24
Motor functioning	GPT–dominant hand (s)‡§	300–0	300–55	97.0	−1.5±1.3	44
	Unimanual programming	0–∞	1–22	11.3	NA	...
	Trails A–time (s)‡§	180–0	180–14	61.1	−1.6±1.3	50
Executive functioning	MWCST–total correct	0–36	2–36	24.4	NA	...
	MWCST–% perseverative errors (cut point≥50)‡	100–0	100–0	31.9	NA	23
	Trails B–time (s)‡§	180–0	180–24	120	−1.2±1.5	38
Visual-spatial functioning	RCFT Copy‡§	0–36	1.5–36	30.2	−0.8±3.0	25
	WAIS-R Block Design§	0–51	0–46	18.9	−0.6±1.0	10
	WMS-R Visual Reproduction Copy‡	0–41	15–41	35.1	NA	...
Language functioning	Boston Naming Test§	0–60	11–60	43.15	−1.4±1.7	51
	Token Test	0–163	2–163	151.94	−0.3±1.6	15

CalCAP indicates California Computerized Assessment Package; CVLT, California Verbal Learning Test; GPT, Grooved Pegboard Test; MWCST, Modified Wisconsin Card Sorting Test (Nelson's version); OMC, Short Blessed Test of Orientation, Memory and Concentration; RCFT, Rey Osterrieth Complex Figure Test; TICS, Telephone Interview of Cognitive Status; Trails A, Trailmaking Test–Part A; Trails B, Trailmaking Test–Part B; WAIS-R, Wechsler Adult Intelligence Scale–Revised; and WMS-R, Wechsler Memory Scale–Revised. Refer to text for methods used to calculate domain summary scores. Values are mean±SD.

*Based on published normative data.

†An alternate version of the CVLT (“Aprendizaje Verbal: Palabras”) was used for Spanish-speaking subjects.

‡Tests requiring transformations for significant skewness.

§Significantly below normative reference group ($P \leq 0.006$, 1-sample t test).

||Percent of subjects falling ≥ 2 SD below the normative sample mean or cut point.

follow-up bias among subjects alive at 3 months by comparing selected demographic, clinical, and radiographic variables between patients who had neuropsychological testing and those who did not. One-way ANOVA was used to compare continuous variables, and the χ^2 test was used to compare categorical variables.²⁰ Student's 1-sample t test was used to test normative Z scores for significant deviations from zero.²⁰

After continuous variables had been dichotomized at the median, all demographic, clinical, and radiographic variables were tested for univariate associations with cognitive domain scores by use of ANOVA models, with cognitive scores as the dependent measure. To evaluate the effect of aneurysm location, we compared subjects within each anatomic category with all other patients. ANCOVA models were used to control for demographic bias in situations in which a specific demographic variable was significantly associated with both a clinical or radiographic variable and a particular domain score. We used Levene's test to verify that the ANOVA assumption of equal variance was satisfied for both levels of the independent variables.²¹ When it was not, univariate associations were tested with t tests without assuming equal variance.²⁰

To identify independent predictors of cognitive outcome, we used 2-block forward-stepwise multiple linear regression (listwise deletion) with cognitive domain scores as the dependent variable.²⁰ Demographic variables that exhibited univariate associations were forced in on block 1; candidate clinical and radiographic variables

with significant univariate associations were then entered in a forward stepwise fashion in block 2. For pathophysiological categories exhibiting more than one significant univariate association, the most significant variable was selected. Significance was judged at a value of $P < 0.05$ for all analyses.

Results

Follow-Up Bias

Figure 1 shows the follow-up status of the 326 patients enrolled in the study. Of 248 patients (76%) known to be alive at 3 months, 212 (85%) were evaluated with the basic outcomes assessment, and 113 (45%) underwent neuropsychological testing. Patients who underwent neuropsychological testing were significantly younger, less often white, and had better 3-month modified Rankin scores than those who did not (χ^2 test, Table 2). The 2 groups were similar with regard to clinical disease severity, complications, and 14-day TICS scores. The mean follow-up interval was 107 ± 21 days.

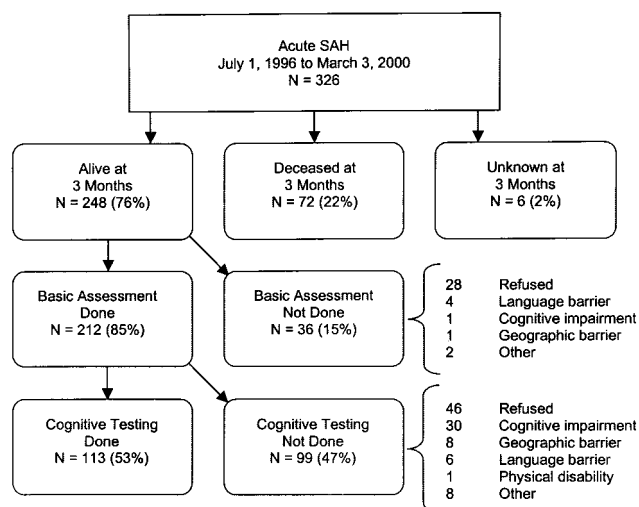


Figure 1. Schematic of follow-up rates.

Study Population

The 113 patients who underwent neuropsychological testing ranged in age from 19 to 86 years (Table 2). Forty-nine (43%) were Hispanic; 48 (43%) were white, non-Hispanic; 14 (12%) were black, non-Hispanic; and 2 (2%) were Asian. Sixty-seven (59%) of the participants were native English

speakers, and 14 (12%) spoke English fluently as a second language. Of 103 patients (91%) with an aneurysm, the location was the anterior circulation in 85 and posterior circulation in 18; 89 were treated with surgical clipping, 13 with coil embolization, and 1 was not treated. Infarction occurred in 31 patients (27%); 12 cases were caused by vasospasm, 11 occurred as a direct complication of clipping or coiling, and 8 resulted from other causes or an unknown mechanism. Global cerebral edema was present on the admission CT scan in 4 patients and was visualized on follow-up scans (all before day 12) in 5.

Neuropsychological Performance

Performance of the study population was significantly below that of published norms in all of the cognitive tests we evaluated with the exception of the Token test (1-sample *t* test, Table 1). The proportion of subjects who scored in the impaired range (>2 SD below the normative mean) on each test ranged from 10% to 50%. The highest frequency of impairment was in tests of verbal memory and motor functioning (all >40%), and the lowest in tests of visual-spatial functioning (all <25%). In the majority of cases, Z scores for each test had a bimodal distribution, with one peak at or above the normative level and another in the impaired range.

TABLE 2. SAH Subjects Alive at 3 Months Who Did or Did Not Undergo Neuropsychological Testing

Variable	Neuropsychological Testing (n=113)	No Neuropsychological Testing (n=135)	P
Demographics			
Age, y	49.3±13.0	54.6±15.4	0.005
Women	77 (68)	80 (59)	NS
White	48 (42)	81 (60)	0.006
Education, y	11.8±4.3	12.3±3.6	NS
Fluent in English	81 (72)	109 (81)	NS
Clinical			
Admission Hunt-Hess grade			NS
1 or 2	63 (56)	63 (47)	
3	33 (29)	51 (38)	
4	14 (12)	17 (13)	
5	3 (3)	4 (3)	
Hijdra SAH Sum score	12.9±8.6	13.0±7.5	NS
Intraventricular hemorrhage	49 (43)	58 (43)	NS
APACHE-2 score	7.9±5.2	8.5±5.4	NS
Posterior circulation aneurysm	18 (16)	35 (26)	NS
Nonaneurysmal SAH	10 (9)	21 (16)	NS
Delayed cerebral ischemia*	23 (20)	25 (19)	NS
14-Day TICS score	27.4±11.8	24.4±13.8	NS
3-Month modified Rankin score			0.001
0 or 1	47 (42)	40 (40)	
2 or 3	60 (53)	37 (37)	
4 or 5	6 (5)	24 (24)	

Values are mean±SD or n (%). P values refer to χ^2 test.

*Refer to Methods for definition.

TABLE 3. Univariate Analysis of Demographic, Clinical, and Radiological Variables Associated With Poor Cognitive Domain Scores

Risk Factor	%*	Cognitive Domain															
		Global Mental Status		Visual Memory		Verbal Memory		Motor Functioning		Reaction Time		Executive Functioning		Visual-Spatial Functioning		Language Functioning	
		F	P	F	P	F	P	F	P	F	P	F	P	F	P		
Demographic																	
Age ≥ 50 y	50	18.0	0.000	39.2	0.000	20.1	0.000	37.2	0.000†	12.0	0.001	13.0	0.000	14.9	0.000	4.80	0.030
Education ≤ 12 y	54	39.0	0.000	20.0	0.000	15.9	0.000	33.3	0.000	21.9	0.000	29.4	0.000	52.3	0.000	38.0	0.000
Nonfluent in English	28	18.2	0.000	11.1	0.000	3.8	0.026	23.0	0.000	12.1	0.000	11.3	0.000†	29.5	0.000	41.2	0.000
Nonwhite ethnicity	58	37.1	0.000	6.2	0.014	11.8	0.001	20.4	0.000	16.8	0.000	42.1	0.000	39.9	0.000	83.7	0.000
Male sex	32	5.8	0.018	14.1	0.000
Clinical condition																	
Admission Hunt-Hess > 2	44	9.6	0.002	4.2	0.042	6.8	0.011	6.0	0.016	5.1	0.026	8.3	0.005
Worst Hunt-Hess > 2	63	4.1	0.046	4.3	0.041
NIHSS > 0 ^F	42	6.4	0.013	5.6	0.020	4.6	0.034	5.1	0.027
Admission GCS < 15	40	5.8	0.018
APACHE-2 physiology > 4	42	4.0	0.049
Focal SAH clot																	
Anterior interhemispheric	10	6.9	0.010	6.7	0.011
Right sylvian	14	5.9	0.017	11.7	0.001	4.2	0.042	13.2	0.000	5.7	0.019	7.2	0.009
Left sylvian	13	5.7	0.019	7.0	0.009	5.7	0.019
Hydrocephalus																	
Treated hydrocephalus ^{E,R}	23	3.9	0.050
Cerebral edema																	
Global edema	8	4.4	0.039	8.6	0.004	6.4	0.013	9.4	0.003	6.6	0.011†	6.4	0.013
Focal edema	23	3.9	0.050
Ischemia																	
Left-sided infarction	18	12.1	0.001	9.6	0.002	14.3	0.000
Any infarction	27	4.9	0.028
Aneurysm location																	
Right sided ^S	29	4.1	0.046
Non-posterior circulation ^{A,G}	84	10.0	0.002	8.4	0.004	14.5	0.000	5.1	0.026	9.0	0.003	10.1	0.002	5.8	0.017
Anterior communicating	24	4.9	0.030

Values refer to differences between domain Z scores in subjects with and without each risk factor by ANOVA or ANCOVA models. Superscript letters indicate adjustment for demographic factors (A, age; E, education; F, fluency in English; R, race/ethnicity; S, sex). Values in bold indicate variables that remained significant ($P < 0.05$) in the multivariate model within each domain.

*Percentage of the study population with the given risk factor.

†Domain scores exhibiting unequal variance between risk factor levels. In these cases, differences were tested with a *t* test, without assuming equal variance.

Univariate Predictors of Cognitive Outcome

All demographic, clinical, and radiographic variables that had a univariate association (ANOVA or ANCOVA) with 1 or more cognitive domain scores are shown in Table 3. All domain scores were significantly worse in patients who were older (>50 years), had less education (≤12 years), were not fluent in English, and were of non-white race/ethnicity.

As expected, poor neurological grade on admission was associated with worse performance on tests of global mental status (GMS) and in 5 of 7 specific cognitive domains. Among clinical and radiographic variables, NIHSS score > 0, thick SAH filling the anterior interhemispheric or sylvian fissures, global cerebral edema, left-sided infarction, and

SAH not related to rupture of a posterior circulation aneurysm were associated with poor performance in GMS and at least 1 other domain (Figures 2 and 3).

Multivariate Predictors of Cognitive Outcome

Clinical and radiographic variables associated with poor cognitive performance in the multiple linear regression analyses are shown in Table 4. Among demographic variables, age ≥ 50 years was most consistently associated with poor test performance, affecting GMS and 5 of 7 specific cognitive domains. The 2 variables that were most predictive of cognitive status with control for demographic factors were radiographic: global edema (4 domains) and left-sided infar-

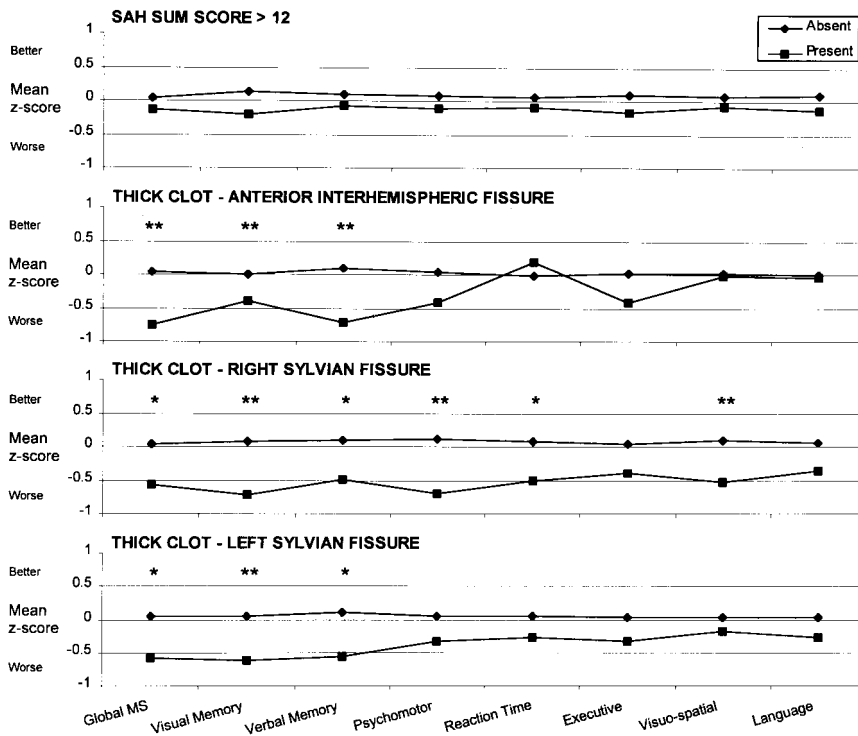


Figure 2. Effect of total amount of SAH and focal clot in specific locations on GMS and cognitive domain scores. Z scores show the relative performance of patients with or without the risk factor in relation to the study sample mean. Positive values indicate better performance. A Z score of 1 represents 1 SD above the sample mean. * $P < 0.05$, ** $P < 0.01$ for differences between groups.

tion (GMS and 2 domains). Other independent predictors of poor cognitive status included Hunt-Hess grade > 2 (executive function), thick SAH filling the anterior interhemispheric fissure (GMS), and non-posterior circulation aneurysm location (verbal and nonverbal memory).

Discussion

We evaluated multiple potential clinical and radiographic risk factors for cognitive dysfunction in a multiethnic cohort of

good-outcome SAH patients. After control for the strong influence that such demographic factors as age and education had on test performance, global cerebral edema and left-sided infarction emerged as the 2 acute disease variables most consistently associated with poor neuropsychological test performance. Other variables associated with cognitive dysfunction included an abnormal neurological examination on admission (Hunt-Hess grade > 2) and thick SAH in the anterior interhemispheric and sylvian fissures, whereas bleed-

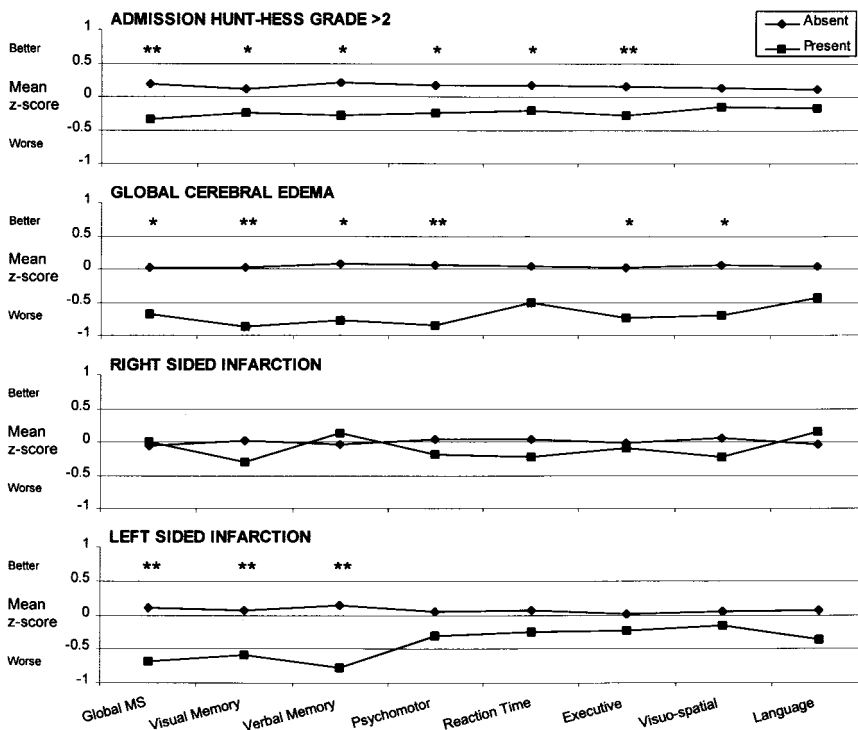


Figure 3. Effect of admission Hunt-Hess grade, global cerebral edema, and right- and left-sided infarction on GMS and cognitive domain scores. Z scores show the relative performance of patients with or without the risk factor in relation to the study sample mean. Positive values indicate better performance. A Z score of 1 represents 1 SD above the sample mean. * $P < 0.05$, ** $P < 0.01$ for differences between groups.

TABLE 4. Multivariate Analysis of Demographic, Clinical, and Radiological Variables Associated With Poor Cognitive Domain Scores

Risk Factor	Cognitive Domain															
	Global Mental Status		Visual Memory		Verbal Memory		Motor Functioning		Reaction Time		Executive Functioning		Visual-Spatial Functioning		Language Functioning	
	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P
Demographic																
Higher age (per year)	-0.015	0.007	-0.023	0.000	-0.018	0.003	-0.026	0.000	-0.012	0.054	-0.019	0.000	-0.011	0.024
Lower education (per year)	-0.050	0.025	-0.040	0.104	-0.037	0.141	-0.028	0.157	-0.073	0.004	-0.036	0.083	-0.081	0.000	-0.054	0.015
Nonfluent in English	-0.196	0.082	-0.139	0.250	-0.026	0.829	-0.297	0.003	-0.140	0.265	-0.061	0.549	-0.157	0.107	-0.245	0.027
Nonwhite ethnicity	-0.432	0.013	-0.068	0.729	-0.295	0.114	-0.215	0.160	-0.215	0.269	-0.776	0.000	-0.343	0.026	-0.773	0.000
Male sex	-0.382	0.008	-0.612	0.000
Clinical/radiographic																
Admission Hunt-Hess>2	-0.363	0.003
Anterior interhemispheric thick SAH	-0.568	0.013
Global edema	-0.783	0.002	-0.674	0.009	-0.645	0.003	-0.511	0.016
Focal edema	-0.624	0.003
Left-sided infarction	-0.504	0.004	-0.621	0.001	-0.736	0.000
Non-posterior circulation aneurysm	-0.522	0.012	-0.683	0.001
Adjusted R ² for entire model	0.515		0.409		0.470		0.539		0.352		0.464		0.548		0.583	

Bold indicates variables that remained significant ($P < 0.05$) in the final multiple linear regression model. Demographic variables that were related to each cognitive domain were forced into the model in block 1, and clinical/radiographic variables were added by a forward stepwise selection procedure in block 2. β -Values (B) represent average change in Z score units for performance in each cognitive domain for patients with the risk factor.

ing from a posterior circulation aneurysm was associated with better cognitive outcomes. These results suggest that interventions aimed at reducing neurological injury due to brain swelling, ischemia, and clot-related hemotoxicity hold the best promise for improving cognitive outcomes after SAH.

Consistent with our understanding of factors that can influence neuropsychological test performance,¹⁰ 4 demographic variables—age, education, ethnicity, and fluency in English—were highly associated with test performance in all cognitive domains, and the strength of these associations generally exceeded those of the disease-related variables we analyzed (Table 3). Importantly, we found that even when test scores were corrected for demographic bias using published normative data, significant associations between demographic factors and cognitive status remained. This type of “residual bias” may explain in part the weak relationship between SAH-related disease severity and cognitive outcome sometimes found in previous studies.⁵ Future studies and clinical trials need to carefully control for the significant effects that demographic bias can have on cognitive test performance after SAH, particularly if culturally diverse populations are studied.

The overall performance of our patients on neuropsychological testing was below normal, with 10% to 50% of patients scoring in the impaired range in each of the specific domains we tested. We observed a bimodal distribution of test scores, with the majority of patients scoring in the normal range and a subset in the highly impaired range. This finding is in agreement with previous observations^{5,22} that cognitive dysfunction after SAH most often reflects severe impairment

in a subset of patients, rather than mild-to-moderate impairment in the majority. Consistent with other studies,^{5,9,22} the highest rates of impairment in our patients were in verbal memory and motor functioning; clinically significant impairment was found in >40% of all tests related to these domains (Table 1).

Poor Hunt-Hess grade on admission (III to V), which reflects neurological dysfunction related to the acute hemorrhage, was associated with impaired function in 6 of 8 cognitive domains in the univariate analysis but retained an association only with executive function in the multivariate analysis (Table 4). Poor neurological grade was also highly correlated with most of the specific acute disease variables we evaluated (eg, quantity of blood, hydrocephalus, complications from ischemia). The fact that clinical grade was not highly predictive of cognitive outcome in the multivariate analysis suggests that secondary insults may play a relatively more important role in the causation of cognitive impairment after SAH than injury at ictus.³

Although a number of earlier studies linked angiographic or TCD-documented vasospasm to cognitive impairment after SAH,^{8,23–25} more recent prospective studies have failed to confirm this association,^{22,26,27} as we did. Improved treatment of vasospasm with the widespread use of nimodipine and HHT in recent years may explain this discrepancy. Others have found a strong association between cognitive dysfunction and CT-documented infarction^{5,22,28} but little or no relationship with clinically diagnosed symptomatic vasospasm,^{22,27} a dissociation also in accord with our findings. We found that left-sided infarction was particularly injurious, as

reflected by its association with impaired GMS and visual and verbal memory in the multivariate analysis. The only other large prospective study of cognitive outcome after SAH that examined the effect of lateralized infarction also found a relationship between left-sided infarction and deficits in verbal memory and language.²⁸ These findings in sum indicate that ischemia after SAH leads to cognitive dysfunction only when it results in infarction. Importantly, $\approx 50\%$ of the infarcts in our cohort resulted from procedural complications related to clipping or coiling, rather than from vasospasm.

One of the most powerful and consistent predictors of cognitive dysfunction in our study was global cerebral edema, which affected 4 of 8 domains in the multivariate analysis. This radiographic finding has not previously been evaluated in studies of cognition after SAH. Global edema was relatively uncommon in our patients, affecting $\approx 10\%$, which may be explained in part by its strong association with mortality.²⁹ Little is known about the pathogenesis of diffuse edema after SAH, but experimental studies suggest that it may be a manifestation of transient global ischemia related to elevated intracranial pressure at the time of bleeding, resulting in microvascular injury, impaired autoregulation, and rebound hyperemia.^{30,31} Clinical studies are needed to further elucidate the pathogenesis of global cerebral edema and microcirculatory dysfunction after SAH.

Thick subarachnoid clot completely filling the sylvian and anterior interhemispheric fissures exhibited univariate associations with cognitive dysfunction in 6 domains, with the strongest impact on GMS, and visual and verbal memory. By contrast, the total amount of SAH had no relationship with cognitive outcome, which corroborates the results of many other studies^{5,26,32}; exceptions include observed associations with impaired executive function²⁷ and verbal memory.³³ The only other study investigating the impact of SAH location on cognitive outcome found impaired working memory (forward digit span task) after 12 months in patients with thick blood in the left sylvian fissure.⁵ These findings suggest that cognitive dysfunction resulting from exposure of the brain to subarachnoid blood occurs most often when it is in contact with the basal frontal and perisylvian cortex. Interventions directed toward reducing the burden of subarachnoid blood (ie, cisternal clot lysis) or the extent of secondary perihematomal inflammation may result in improved neurological outcomes and deserve further study.

Many investigators have evaluated the effect of aneurysm location on cognitive function after SAH,^{5,7–9,23,24,26,28,32,34–36} but few have reported significant associations; aneurysms of the anterior communicating artery,³⁴ vertebrobasilar system,⁸ and left anterior circulation⁹ have previously been associated with poor cognitive outcome. In our study, posterior circulation aneurysms were associated with better performance in 7 of 8 domains in the univariate analyses and in both memory domains in the multivariate analysis. Because posterior circulation aneurysms generally result in less SAH coming in contact with the cortical surface of the brain, this may result in less disruption of brain regions involved in cognition. Differences in study methodology, including failure to control for demographic variables and small sample sizes, may

explain why this observation has not been consistently found before.

Acute hydrocephalus was unrelated to 3-month cognitive outcome in our study, as was the presence of ICH or IVH. Studies that have analyzed hydrocephalus have reported both significant^{5,33} and nonsignificant^{35,36} associations with cognitive outcome. In one study, the association between radiographic hydrocephalus and memory impairment was evident 10 weeks after SAH, but not at 1 year.⁵ Evidence regarding the relationship between ICH^{5,33,35} or IVH^{5,33} and cognitive outcome after SAH is also sparse and conflicting.

Several limitations of this study deserve mention. Perhaps the most important is that our follow-up period was only 3 months, and many participants were probably still in the active phase of recovery.^{5,9} Analysis after a longer period of follow-up is needed to determine whether the cognitive deficits we identified persisted in the long term; this will be the subject of a future report. Second, although one study found that a large proportion of SAH patients suffer from role limitations related to physical problems,³⁷ it is unclear to what extent cognitive dysfunction after SAH affects health-related quality of life. Finally, our results may not be applicable to older or more severely disabled SAH patients who cannot undergo neuropsychological evaluation; risk factors that we have not identified may be important for producing more severe levels of brain injury after SAH. Although detailed in-person neuropsychological testing is highly sensitive to subtle cognitive dysfunction, there is a need to develop cognitive tests that are more easily administered and widely applicable to more severely impaired SAH patients.

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Editorial Comment

Continued Progress in Predicting Outcome After Subarachnoid Hemorrhage

Spontaneous subarachnoid hemorrhage (SAH), usually a consequence of aneurysm rupture, has been associated with a high mortality rate soon after ictus (43%) with progression to 57% at 6 months.¹ In order to communicate its clinical severity, Hunt and Hess devised a grading scale for SAH that has since been used as a predictor of morbidity and mortality.² Current treatment for SAH has focused on aneurysm repair to avoid further hemorrhage followed by cerebral blood flow augmentation to minimize vasospasm. Recently, Le Roux and colleagues demonstrated that subsets of poor Hunt-Hess grade patients (IV and V) might obtain favorable outcomes with aggressive treatment.³ Furthermore, they were also able to identify clinical factors and computed tomography (CT) features such as intraventricular hemorrhage, ventriculomegaly, and cerebral low density that heralded a poor

outcome.³ The results of such work provided an early indication of those patients who were salvageable.

For long-term survivors of SAH, physical and cognitive deficits have been commonplace.^{4,5} Such deficits have been observed to interfere with resumption of work and have been exacerbated by psychological impairment.^{5,6} Neuropsychological testing has proven useful in these circumstances by defining the adverse neurobehavioral effects subsequent to SAH.⁷ In their work, Hutter and colleagues were able to define some of the radiographic aspects that were associated with neuropsychological impairment.⁷ It is in this setting that Kreiter and colleagues undertook a prospective evaluation of neuropsychological impairment after SAH to determine early predictive factors for long-term cognitive outcome.

In the previous study, Kreiter et al performed neuropsychological testing at 3 months on 113 of 248 patients who survived SAH. Patients who underwent evaluation were usually younger, non-Caucasians with better modified Rankin scores. The patient population encompassed a broad range of ages and races, and all patients were treated according to current standards for aneurysm occlusion and cerebral blood flow augmentation. After neuropsychological testing, scores were calculated in differing cognitive domains and compared with historical averages. To no surprise, domain scores were worse in older patients, those with less education, and those less fluent in English. A univariate analysis revealed that a poor neurological (Hunt-Hess) grade was associated with impairment in several cognitive domains. Other radiographic (CT) and clinical features linked to poor performance were thick SAH in the anterior hemispheric fissure, global cerebral edema, left cerebral infarction, and the presence of an anterior circulation aneurysm.

Because demographic factors such as age were often commonly associated negative predictors, the authors performed multivariate analyses to exclude the confounding influence of these factors. Their analyses revealed that global cerebral edema and left cerebral infarction were independently associated with poor cognitive function in more than 1 domain. The presence of an anterior circulation aneurysm also appeared to be associated independently with cognitive dysfunction in more than 1 domain while an anterior inter-hemispheric SAH was associated with dysfunction in 1 domain. In contrast, an admission Hunt-Hess grade >2 , although associated with dysfunction in 6 of 8 cognitive domains on univariate analysis, was associated with dysfunction in only 1 domain using multivariate analysis. Unlike prior studies, Kreiter and colleagues did not find a clear negative association with hydrocephalus, intraventricular hemorrhage, or intracerebral hemorrhage.^{3,7}

As expected, Kreiter and colleagues confirmed that poor neurological function (Hunt-Hess grade ≥ 3) on admission was associated with significant impairment at 3 months. However, when confounding demographic factors were removed using multivariate analysis, only global cerebral edema and a dominant hemispheric infarction appeared to play a role in cognitive impairment at 3 months. The authors concluded that secondary insults might have accounted more for neurobehavioral impairment at 3 months than the primary SAH did.

Kreiter et al should be commended in further defining predictive factors for cognitive outcome after SAH. Just as Le Roux and colleagues further defined those patients with poor neurological grades who might benefit from early aggressive treatment,³ Kreiter et al have raised the possibility that aggressive treatment with attention to cerebral edema and ischemia may benefit those who survive SAH. Although these authors mentioned obtaining data at 12 months after SAH, this information was not reported but, it is hoped, will provide the basis for a second study and confirm their earlier results.

Currently, those patients considered “good” outcomes after SAH are often afflicted with cognitive impairment.⁷ Such adverse neurobehavioral effects may preclude the ability to maintain employment.^{4–6} By ascertaining those patients who might be most cognitively affected by SAH, Kreiter and colleagues have begun to define those who might benefit most from aggressive cognitive rehabilitation. In the setting of increasing managed care and reduced health care resources, better recognition of such patients is paramount.

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