Cognitive deficits after recovery from thrombotic thrombocytopenic purpura

April S. Kennedy, Qurana F. Lewis, James G. Scott, Johanna A. Kremer Hovinga, Bernhard Lämmle, Deirdra R. Terrell, Sara K. Vesely, and James N. George

BACKGROUND: Patients with apparent complete recovery from thrombotic thrombocytopenic purpura (TTP) often complain of problems with memory, concentration, and fatigue.

STUDY DESIGN AND METHODS: Twenty-four patients who were enrolled in the Oklahoma TTP-HUS Registry for their initial episode of TTP, 1995-2006, and who had ADAMTS13 activity of less than 10 percent were evaluated for a broad range of cognitive functions 0.1 to 10.6 years (median, 4.0 years) after their most recent episode. At the time of their evaluation, they had normal physical and Mini-Mental State Examinations and no evidence of TTP.

RESULTS: The patients, as a group, performed significantly worse on 4 of the 11 cognitive domains tested than standardized US data from neurologically normal individuals adjusted for age, sex, and education ($p < 0.05$). These four domains measured complex attention and concentration skills, information processing speed, rapid language generation, and rote memorization. Twenty-one (88%) patients performed below expectations on at least 1 of the 11 domains. No clear patterns were observed between cognitive test results and patients' characteristics or features of the preceding TTP, including age, occurrence of severe neurologic abnormalities, multiple episodes, and interval from an acute episode.

CONCLUSION: Patients who have recovered from TTP may have persistent cognitive abnormalities. The abnormalities observed in these patients are characteristic of disorders associated with diffuse subcortical microvascular disease. Studies of larger patient groups will be required to confirm these preliminary observations and to determine patient characteristics that may contribute to persistent cognitive abnormalities.

Thrombotic thrombocytopenic purpura (TTP) is a disorder of systemic microvascular thrombosis characterized by acute episodes and complete remissions.[1] Before effective therapy, mortality was 90 percent;[2] introduction of plasma exchange treatment reduced mortality to 22 percent.[3] Recovery is assumed to be complete except for the risk for relapse and the uncommon occurrence of persistent neurologic or renal abnormalities.[1] However, in spite of normal physical examinations and laboratory data, many patients do not feel that they have recovered completely. Difficulties with memory, concentration, and endurance are consistent concerns expressed at patient support group meetings.[4,5] These symptoms have been validated by documentation of deficits of health-related quality of life (HRQoL) measured by the Short-Form 36 (SF-36)

ABBREVIATIONS: HRQoL = health-related quality of life; HUS = hemolytic-uremic syndrome; MMSE = Mini-Mental State Exam; OPIE-III = Oklahoma Premorbid Intelligence Estimate-III; SF-36 = Short-Form 36; TTP = thrombotic thrombocytopenic purpura.

From the Department of Medicine and Department of Psychiatry & Behavioral Sciences, College of Medicine, and the Department of Biostatistics and Epidemiology, College of Public Health, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma; and the Department of Hematology and Central Hematology Laboratory, Inselspital, Berne University Hospital and University of Berne, Berne, Switzerland.

Address reprint requests to: James N. George, MD, or Sara K. Vesely, PhD, Department of Biostatistics and Epidemiology, The University of Oklahoma Health Sciences Center, Room CHB 358, P.O. Box 26901, Oklahoma City, OK 73126-0901; e-mail: james-george@ouhsc.edu or sara-vesely@ouhsc.edu.

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Health Survey.[6] After recovery from TTP, patients, as a group, performed less well on all eight domains of the SF-36 compared to US population data; no significant improvement occurred across 5 years after their acute episode.[6]

We hypothesized that the patients' symptoms that were apparent in the documented deficits of HRQoL may be caused by persistent cognitive abnormalities. To explore this hypothesis, we systematically reviewed published reports to search for descriptions of cognitive abnormalities in patients who had recovered from TTP. We also performed neuropsychological testing on selected patients who had recovered from TTP without apparent physical deficits or dementia and who were functionally independent in their normal work and daily activities. Neuropsychological testing is a specialty assessment designed to evaluate neurologic functioning using tests of cognitive and motor ability. We anticipated that cognitive domains required for complex attention, concentration skills, and high level memory functions may be affected because these are characteristically abnormal in disorders with diffuse microvascular subcortical lesions. This pattern of deficit has been demonstrated in neurologically normal individuals with untreated hypertension[7] and also in patients with sickle cell disease[8] and multi-infarct dementia.[9]

MATERIALS AND METHODS

Systematic literature review

Ovid software was used to search the Medline database on December 1, 2008. English language articles containing a TTP-related Medical Subject Heading (MeSH) and/or key word in the title or available text [*thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome, TTP-HUS*] and also a Medical Subject Heading (MeSH) and/or key word related to cognitive function in the title or available text [*mental health, cognitive, delirium, dementia, amnestic, anxiety, depression, quality of life*] were identified. Retrieved articles were reviewed to identify data on adult patients described as having TTP or hemolytic-uremic syndrome (HUS) who were also described as having cognitive abnormalities.

The Oklahoma TTP-HUS registry

The Registry includes all consecutive patients for whom the Oklahoma Blood Institute is requested to provide plasma exchange treatment for patients with a clinical diagnosis of TTP or HUS.[10,11] The Oklahoma Blood Institute is the sole provider of plasma exchange services for all hospitals in 58 of the 77 Oklahoma counties. Therefore, the Registry is an inception cohort of all consecutive patients within a defined geographic region in whom the diagnosis of TTP or HUS was established and a decision to initiate plasma exchange treatment was made. Because the Registry provides additional information and support for patients and their families and involves no change of management, all patients have consented to enroll. Severe neurologic abnormalities were defined as coma, stroke, seizure, or focal abnormalities.[10] Serum for ADAMTS13 assays was collected immediately before the first plasma exchange procedure. ADAMTS13 activity was measured by quantitative immunoblotting of proteolyzed von Willebrand factor multimers;[12,13] severe ADAMTS13 deficiency was defined as less than 10 percent activity.[1] Since this study only involves adults and since these syndromes in adults, with or without renal failure or neurologic abnormalities, are commonly known as TTP,[1] we describe patients in this report as having TTP. The Oklahoma TTP-HUS Registry is approved by the institutional review boards of the University of Oklahoma Health Sciences Center and each participating hospital.

Neuropsychological testing

The Folstein Mini-Mental State Exam (MMSE)[14] was used to screen for dementia and to determine eligibility for proceeding with the neurocognitive evaluation. The MMSE has a maximum score of 30; individuals with scores below 24, indicating the presence of overt dementia, were excluded from this study because the specific aim was to assess patients who were functionally independent in their normal work and daily activities.[14] Preillness intellectual level was estimated by the Oklahoma Premorbid Intelligence Estimate-III (OPIE-III) prediction formula, which uses both demographic data and measures from the postillness performance on tests of vocabulary and matrix reasoning subtests of the Wechsler Adult Intelligence Scale-III that are known to be resistant to changes subsequent to neurologic injury.[15-17] The expected mean and median of the OPIE-III are both set at 100 with a standard deviation (SD) of 15, comparable to the standard IQ test.

The cognitive tests used in this study were selected to sample a broad range of cognitive functions across a comprehensive set of cognitive domains. The battery of tests chosen assessed neuropsychological functioning in intelligence, memory, language, executive/reasoning skill, attention, visual spatial perceptual function, information processing speed, and motor functioning. The tests were specifically selected for this study to assess those deficits commonly seen in disorders with diffuse microvascular subcortical lesions. Tests were also performed to assess domains that should not be affected by diffuse microvascular subcortical lesions, but would be affected by severe brain injury. The functional domains that were predicted to be abnormal, before the study was initiated, were complex attention and concentration, information

processing speed, high-level language functioning, and memory as measured by 4 of the 11 tests: complex attention and sequencing, manual dexterity, rapid language generation, and list learning. Table 1 lists the specific tests administered, classified by the domain of functioning.

Altogether, there were 23 individual tests used to assess 11 domains of cognitive function. Although the tests of list learning and semantic memory are both measures of new learning and memory, they were used as independent tests for this study. List learning is a memory task that requires rote memorization of episodic information (i.e., a list of words presented at different times). Semantic memory (i.e., story recall) requires making sense of a story and thus is facilitated by one's semantic knowledge as well as ability to problem solve, organize information, and use internal thoughts to facilitate recall. Because we postulated that our patients' cognitive problems would be subtle, we anticipated that our patients would be more vulnerable to abnormalities of list learning while semantic memory would be preserved.

Tests were administered in standardized fashion by two of the authors (ASK, QSL), who were trained by a board-certified neuropsychologist (JGS); they observed the administration and scoring of the tests and then they were observed administering and scoring the tests until the neuropsychologist was confident that the testing was performed in a standardized, structured manner. Tests were administered in one assessment session, which required approximately 2.5 hours to complete. Tests were scored using normative data, which included adjustments for age, sex, and also education where appropriate to reduce the potential effect of these factors in assessing subtle changes in cognition in our subjects' performance. Citations describing the generation of the normative data for each test are provided in Table 1.

Statistical analysis

Each subject's raw score on each test was converted to a standardized score based on normative data generated from neurologically normal population values according to the subject's age and sex and also education level where appropriate (Table 1). Patients' standardized scores were then converted to a standardized metric (a Z score) with a mean value of 0 and a SD of 1. Performance of individual patients on a cognitive test was defined as below expectations if the score was 1 SD or more below the mean of 0, which is at or below the 16th percentile of the US normative population. Individual scores 2 SDs or more below the mean of 0 are at or below the 2nd percentile of the US normative population. The median value of the standardized Z scores for the 24 patients on each test was expected to be 0 if the cognitive performance was equivalent to the normative population. Median rather than mean was used since the distribution of the TTP patient population may not be normal, based on the appearance of our sample data of 24 patients. The signed-rank test was performed to determine if the median patient population scores were different from the median normal score of 0. Confidence intervals (CIs) around the median were calculated using a distribution-free method. All statistical tests were performed using computer software (SAS, Version 9.1, SAS Institute, Cary, NC); an alpha of 0.05 was used.

RESULTS

Systematic literature review

The literature search identified only 31 articles. Review of the titles and abstracts as well as the texts of selected articles identified only one case report published in 1984 of a 55-year-old man who had a psychiatric disorder characterized by depression and paranoia as well as cognitive deficits after recovery from TTP.[18] No other articles described the presence of symptoms of cognitive impairment among adult patients who were functioning independently in their normal work and daily activities after recovery from TTP, comparable to the current study. One recent systematic review of randomized trials for plasma exchange treatment of TTP was identified by this search, which stated that no studies had measured patients' quality of life.[19]

Patients

The Oklahoma Registry enrolled 360 patients from January 1, 1989, through June 30, 2006, the date when the patient cohort for cognitive testing was selected. Selection of patients for this study is presented in Fig. 1. The goal of patient selection was to include patients who were documented to have ADAMTS13 deficiency at the time of presentation with their initial episode of TTP and who were currently functioning independently in their normal work and daily activities. The inclusion criterion of ADAMTS13 deficiency served to support the diagnosis of TTP and also to minimize heterogeneity among the selected patients. Patients who were less than 18 years old at the time of their enrollment, who were initially enrolled in the Registry at the time of a relapse, who were diagnosed by renal biopsy rather than clinical features, or who enrolled before November 13, 1995, the date when samples were routinely collected for ADAMTS13 measurements, were excluded. Of the 234 remaining patients, ADAMTS13 activity was measured in 215 (92%), 41 (19%) of the 215 patients had ADAMTS13 activity of less than 10 percent, and 29 (71%) of the 41 were currently alive. Seven patients had died during their first episode of TTP, 2 patients had died during their second episode, and 3 patients had died of causes unrelated to an episode of TTP.

Of the 29 living patients, 24 (83%) were included in this study. Of the 5 patients not included in this study, 1

TABLE 1. Neurocognitive tests used to evaluate patients who have recovered from TTP*

Tests	Cognitive domains	Description	Reference for test performance	Reference for test scoring
Conners Continuous Performance Test, Reaction Time	Reaction time	Provides a precise measure of reaction time of processing speed.	Conners and Jeff,[24] Conners[25]	Conners[25]
Conners Continuous Performance Test, Omission Errors Conners Continuous Performance Test, Commission Errors	Simple sustained attention	Evaluates sustained attention and problems related to inattention and impulsivity.		
Trail Making Test, Part A Symbol Digit Modalities Test (oral)	Complex attention, sequencing/concentration skills	Evaluates speed of visual search, attention, rapid alternation of attention, and visual-motor functioning.	Reitan,[26] Smith[27]	Smith,[27] Heaton et al.[28]
Grooved Pegboard Test	Manual dexterity/information processing speed	Evaluates manual fine motor speed with the right and left hands.	Harley et al.,[29] Klove[30]	Heaton et al.[28]
Hooper Visual Organization Test	Visual perceptual skills	Examines ability to visually synthesize fragmented images into whole perceptions.	Hooper[31]	Hooper[31]
Phonemic Fluency Test Semantic Fluency Test	Rapid language generation	Measures rapid verbal fluency, the ability to generate words based on a set of rules; and assesses high-level language function.	Benton and Hamsher[32]	Heaton et al.[28]
California Verbal Learning Test-II, short delay free recall California Verbal Learning Test-II, long delay free recall California Verbal Learning Test-II, total across trials	List learning/rote memorization	Word list test of memory and learning to assess immediate recall, rate of learning across trials, and short- and long-term retention of a word list.	Delis et al.[33]	Delis et al.[33]
Wechsler Memory Scale-Revised, Logical Memory I Wechsler Memory Scale-Revised, Logical Memory II	Semantic memory	Measures immediate and delayed recall of semantic information presented in paragraph form.	Wechsler[34]	Wechsler[34]
Wechsler Memory Scale-Revised, Visual reproduction I Wechsler Memory Scale-Revised, Visual reproduction II	Visual memory	Measures immediate and delayed visual memory.	Wechsler[34]	Wechsler[34]
Delis-Kaplan Executive Function Battery, Design Fluency subtest WAIS-III Matrix Reasoning subtest Trail Making Test, part B	Executive functioning, reasoning	Assesses cognitive flexibility, alternating attention and reasoning skills.	Delis and Kaplan,[35] Delis et al.[36]	[15] Heaton et al.,[28] Klove[30]
Wechsler Adult Intelligence Scale-III, Vocabulary and Matrix Reasoning subtests	Intellectual functioning	Two components, matrix reasoning and vocabulary, measure verbal and nonverbal functions. These provide an estimate of the full-scale IQ and have been shown to be resistant to change secondary to ischemic insult, thereby providing a reliable estimate of premorbid level of functioning.	Wechsler,[15] Schoenberg et al.[16,17]	Wechsler[15]

* The tests used to assess 11 domains of cognitive function are described. Tests are listed in the order that they were performed during the patient evaluations. Citations are provided both for the original source describing the test performance as well as for generation of the normative data used for test scoring.

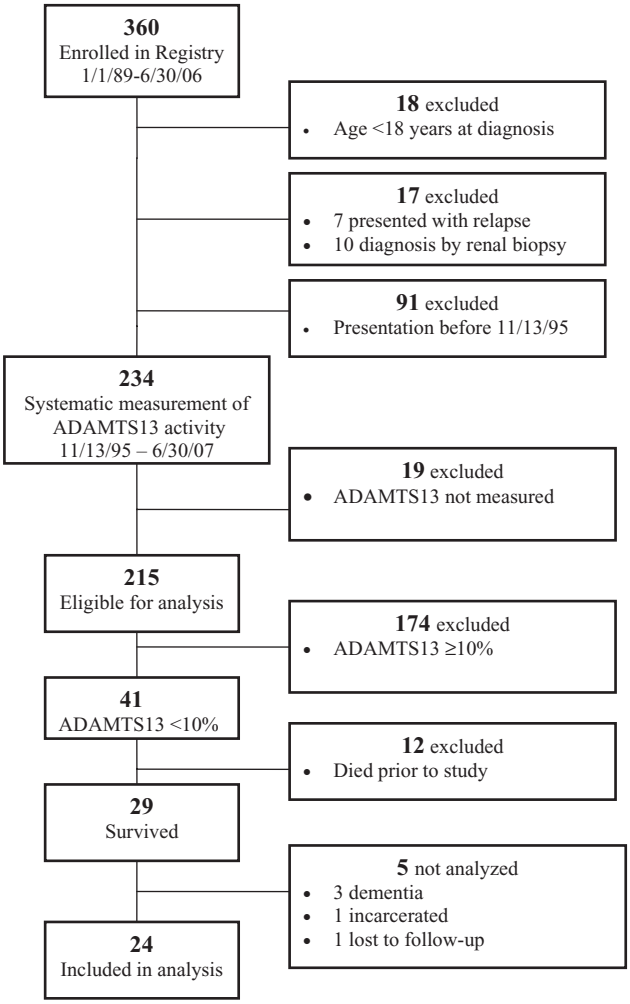

Fig. 1. Selection of patients for analysis.

TABLE 2. Characteristics of 24 patients who had recovered from TTP and were evaluated by neurocognitive tests*

Age (years; median, range)	
At initial episode	39 (19-63)
At time of cognitive testing	44 (20-64)
Race	
White	14 (58%)
Black	9 (38%)
Native American	1 (4%)
Sex (women)	21 (88%)
Education (years; median, range)	14 (10-16)
MMSE (median, range)	30 (26-30)
OPIE-III (median, range)	99.4 (78.3-119.0)
Number of relapses	
0	16 (67%)
1	4 (17%)
2	1 (4%)
4	3 (12%)
Severe neurologic abnormalities during the initial episode	10 (42%)
Interval between most recent episode and cognitive testing (years; median, range)	4.0 (0.1-10.6)
Laboratory evaluation at time of cognitive testing	
Hct (%; median, range)	39% (31-51%)
PLT count ($\times 10^9$/L; median, range)	303 (81-518)
ADAMTS13 activity at time of cognitive testing	
51%-100%	13 (54%)
21%-50%	6 (25%)
10%-20%	2 (8%)
<10%	3 (13%)

* Education years indicate completion of high school at 12 years and completion of college at 16 years. For the MMSE, the maximum score was 30. For the OPIE-III, the expected median is 100 with a SD of 15, comparable to the standard IQ test.

has been lost to all follow-up efforts, 1 was incarcerated throughout the period of our testing, and 3 patients were excluded because of dementia. Overt dementia was present in 2 patients as assessed by their family and health care providers, both were older than the oldest patient included in this study, and neither had any apparent mental status changes before their TTP. One of these 2 patients, who was 71 years old at the time of her initial diagnosis of TTP and 78 years old at the time of this study, had a stroke during her first of two episodes of TTP with left hemiplegia and persistent disability. The other patient was 68 years old at the time of her initial episode of TTP and 75 years old at the time of this study; she had no apparent neurologic abnormalities during her one episode of TTP. The third patient who was excluded because of dementia was initially evaluated for this study but was excluded because her MMSE score was 23. She was 39 years old at this time and had been in good health at the time of her one episode of TTP 6 years previously. During her episode of TTP she had a left cerebral infarction causing her to become obtunded and aphasic; she recovered without physical disability but with persistent speech difficulties.

The 24 patients included in this study all had a normal MMSE. Their MMSE performance scores were 26 to 30 (median, 30), documenting their essentially normal cognitive functioning. These patients were completely independent, performing their normal work and routine daily activities. Although their preillness baseline cognitive functioning was not available, the results of the OPIE-III were normal, consistent with our clinical impression that our patients' intellectual function was normal before their episode of TTP (Table 2).

Characteristics of the 24 included patients are presented in Table 2. Age, race, and sex were similar to all patients with TTP associated with severe ADAMTS13 deficiency.[20] The median education level of 14 years was equivalent to completion of 2 years of college. Twenty-two (92%) patients had completed high school education, compared to the mean rates of 81 percent in Oklahoma and 80 percent in the US; 4 (25%) patients had completed college, compared to 20 percent in Oklahoma and 24

percent in the United States.[21] One-third of patients had had multiple acute episodes of TTP. Neuropsychological testing was performed 0.1 to 10.6 years (median, 4.0 years) after recovery from their most recent acute episode, 0.2 to 10.8 years (median, 5.0 years) after recovery from their initial episode. Among the 10 patients who had severe neurologic abnormalities at the time of their acute episodes of TTP, 6 had only transient focal abnormalities, 3 had seizures in addition to transient focal abnormalities, and 1 patient only had seizures. No patients had stroke or coma. At the time of the cognitive evaluation, all patients had a complete history, specifically asking about symptoms or signs that may suggest TTP activity, and physical examination. All patients' physical examinations were normal, no patients had neurologic abnormalities, and there was no evidence for TTP. One patient was anemic (hematocrit [Hct], 31%) due to iron deficiency after gastric bypass surgery for obesity; her platelet (PLT) count was 350×10^9 per L and her ADAMTS13 activity was 80 percent; no other patients were anemic. One patient has had persistent mild thrombocytopenia (PLT count, 81×10^9/L) due to cirrhosis and hypersplenism caused by nonalcoholic steatohepatitis related to diabetes mellitus and obesity; her Hct was 35 percent and her ADAMTS13 activity was 100 percent; no other patients had thrombocytopenia. One patient has had persistent thrombocytosis after splenectomy for her TTP in 2000. ADAMTS13 activity at the time of the cognitive testing was decreased (activity, ≤50%) in 11 (46%) patients; none of these 11 patients had thrombocytopenia or anemia. Three patients had severe ADAMTS13 deficiency, activity of less than 10 percent; 1 of these patients had a strong inhibitor (>2 Bethesda Units), and no inhibitor activity was present in the other 2 patients although each of these patients had had strong inhibitors at the time of their initial episode. There was no apparent correlation between the time since the most recent acute episode of TTP and ADAMTS13 activity ($r = -0.18$, $p = 0.393$). For the 3 patients with persistent severe ADAMTS13 deficiency, the interval between their most recent acute episode and the neuropsychological testing was not less than the interval for the other 21 patients; their neuropsychological assessments were performed 4.6, 6.4, and 10.6 years after their most recent acute episode.

Cognitive evaluation

The median score of the 24 patients was significantly different than the median normal score of 0 for 4 of the 11 domains: complex attention and sequencing, manual dexterity, rapid language generation, and list learning ($p < 0.05$; Fig. 2, Table 3). This indicates a group performance significantly worse than the US population norms for neurologically normal subjects. Eighteen (75%) of the 24 patients performed below expectations on one or more of these 4 domains, defined by scores greater than 1 SD below the mean, placing them at or below the 16th percentile of the US population. Five of these 18 patients were moderately or severely impaired on one or more of these 4 domains, defined by scores greater than 2 SDs below the

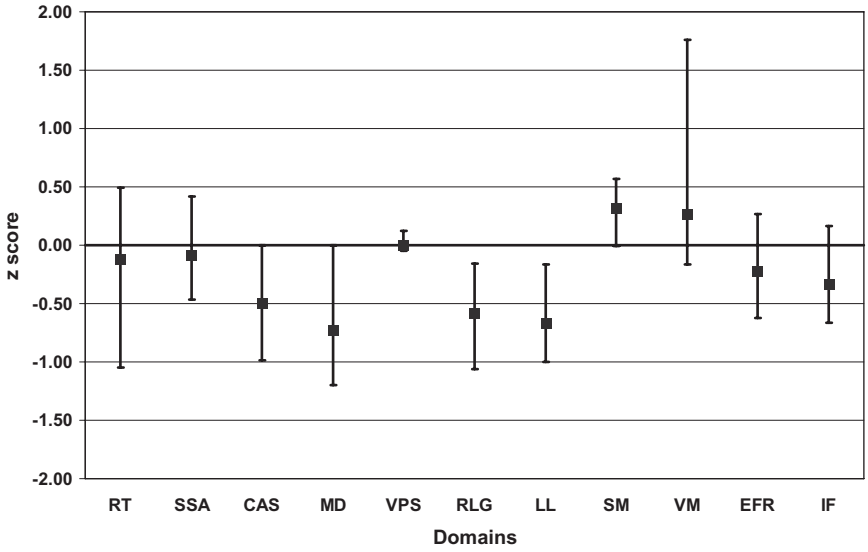

Fig. 2. The data presented in Table 3 are presented graphically for the results of the tests of each of the 11 cognitive domains. The results are presented as the median value and the 95 percent distribution-free CIs for each domain. The median normal score is 0 for each domain. Abbreviations for the cognitive domains are as follows: RT = reaction time; SSA = simple sustained attention; CAS = complex attention/sequencing; MD = manual dexterity; VPS = visual perception skills; RLG = rapid language generation; LL = list learning; SM = semantic memory; VM = visual memory; EFT = executive functioning/reasoning; IF = intellectual functioning.

TABLE 3. Results of neurocognitive tests in 24 patients who had apparent complete recovery from TTP*

Neurocognitive test domain	Median patient score	p Value (median patient score compared to 0)	Patients performing ≤16th percentile	Patients performing ≤2nd percentile
Reaction time	−0.12	0.719	8 (33%)	
Simple sustained attention	−0.08	0.719	6 (25%)	3 (13%)
Complex attention, sequencing	−0.50	0.002	7 (29%)	1 (4%)
Manual dexterity	−0.73	0.007	10 (42%)	3 (12%)
Visual perceptual skills	0.00	0.883	0 (0%)	
Rapid language generation	−0.58	0.016	8 (33%)	
List learning	−0.67	<0.001	9 (38%)	3 (12%)
Semantic memory	+0.32	0.149	1 (4%)	
Visual memory	+0.27	0.071	4 (17%)	
Executive function/reasoning	−0.22	0.234	3 (13%)	
Intellectual functioning	−0.33	0.108	5 (21%)	

* Patient performance on each of the 11 domains of cognitive function. The patient's individual raw scores on each test were standardized to a Z score with a mean of 0 and a SD of 1. The p values compare the median of the standardized scores (Z scores) of the 24 patients as a group to the median normal score of 0. Patients who scored 1 SD or more below the mean are at or below the 16th percentile. Patients who scored 2 SDs or more below the mean are at or below the 2nd percentile. Patients who scored 2nd percentile or less are also counted in the column designated as patients 16th percentile or less.

mean, placing them at or below the 2nd percentile of the US population. Since our description of performance below expectations was a score greater than 1 SD below the mean, at or below the 16th percentile of the US population, for any 1 domain it would be expected that 16 percent (or 4 of our 24 patients) would be impaired; for 7 of the 11 domains 5 (21%) to 10 (42%) patients performed below expectations. Twenty-one (88%) patients performed below expectations on at least 1 of the 11 domains; 4 (17%) patients performed below expectations on 6 to 8 of the 11 domains; 3 (13%) patients did not perform below expectations on any of the 11 domains (Table 4).

Performance on the four cognitive domains for which the group as a whole scored significantly less than the median normal value of 0 are illustrated together with individual patient characteristics in Table 4. No formal statistical analyses were performed since there were data on only 24 patients and there were multiple characteristics that may have been important. Examination of the individual patient data suggests that cognitive test performance was not related to the patient's age or to the time since the most recent episode of TTP. There was also no clear relation between cognitive performance and the number of episodes; 11 of 16 patients who had no relapses performed below expectations on one or more of these four domains while 1 patient with four relapses did not perform below expectations on any of these four domains. Among the 10 patients with severe neurologic abnormalities during their acute episode of TTP, 8 performed below expectations on one or more of these four domains; among the 14 patients without severe neurologic abnormalities, 10 performed below expectations on one or more of these four domains. The 3 patients with persistent severe ADAMTS13 deficiency (<10%) all performed below expectations on one or more of these four domains; 9 of the 13 patients with normal ADAMTS13 activity (>50%) performed below expectations on one or more of these four domains. Treatment was not standardized and therefore no relation to treatment of the acute episode could be assessed.

DISCUSSION

Many of our patients have expressed concerns that they are not as capable, mentally or physically, as they were before their episode of TTP.[4,5] We have confirmed the validity of these symptoms by documenting significant long-term deficits of HRQoL.[6] To explore the basis for our patients' symptoms, we evaluated a broad range of cognitive functions in 24 patients who had severe ADAMTS13 deficiency at the time of their initial episode of TTP. If cognitive deficits occur after recovery from TTP, they are subtle and not widely recognized because we identified no previous reports of these abnormalities, with the exception of a case report from 1984 of a man with

TABLE 4. Individual patient characteristics and results of cognitive tests*

Age (years)	Relapses (number)	Severe neurologic event during acute episode	ADAMTS13 activity (%) at time of cognitive assessment	Years since most recent episode	Cognitive test results			
					Complex attention, sequencing	Manual dexterity	Rapid language generation	List learning
38	2	Yes	>50	<1	– – –	– –	–	– – –
33	0	No	>50	<1	– –	–	–	– –
62	4	Yes	21-50	<1	–	– –	– –	–
21	0	No	>50	<1	–	+	– –	– –
64	0	Yes	21-50	<1	–	–	– –	–
25	0	No	11-20	<1	+	–	–	– –
20	0	No	>50	1	+	+	+	–
49	1	No	>50	2	+	– –	– –	–
42	0	No	>50	3	–	+	+	+
48	0	Yes	>50	3	–	–	–	+
58	1	Yes	21-50	3	–	– – –	–	–
45	0	Yes	21-50	4	+	+	+	+
50	4	Yes	>50	4	– –	– –	– –	+
58	0	No	>50	5	+	– –	–	–
24	0	No	<10	5	– –	– –	–	–
25	0	No	>50	5	+	+	+	–
38	0	No	>50	5	– –	– – –	– –	– – –
43	0	Yes	11-20	5	–	+	+	– – –
44	0	No	21-50	6	–	–	–	– –
29	0	No	<10	6	– –	–	–	– –
32	4	No	21-50	6	–	+	+	–
52	1	Yes	>50	7	–	– –	–	–
49	0	Yes	>50	10	–	– – –	– –	+
52	1	No	<10	11	– –	–	– –	– –

* Data are presented for the demographic and clinical characteristics of the 24 individual patients and their standardized scores on the tests of the four domains for which the group was abnormal. The results of the tests for these four domains are presented as [1] +, if the score was 0 or greater; [2] –, if the score was less than 0 but less than 1.0 SD below the mean of 0; [3] – –, if the score was 1.0 or greater but less than 2.0 SDs below the mean of 0, indicating a score at or below the 16th percentile; or [4] – – –, if the score was 2.0 SDs or greater below the mean of 0, indicating a score at or below the 2nd percentile. Scores 1.0 SD or more below the mean of 0 are described as performance below expectations.

psychiatric disorders and cognitive deficits after recovery from TTP.[18]

ADAMTS13 deficiency was selected as an inclusion criterion for this study because 1) it supported the diagnosis of TTP, 2) it provided a patient group that was less heterogeneous than if we had included all patients in our Registry, and 3) it provided an appropriate number of patients to study with extensive neuropsychologic tests. However, in our support group meetings[4,5] complaints of problems with memory, concentration, and endurance are also expressed by patients with other apparent etiologies. Our previous study of HRQoL was also not limited to patients who had ADAMTS13 deficiency and there was no apparent difference in the HRQoL results among different categories of patients.[6]

Owing to the preliminary nature of the study, patients were compared to standardized normative data generated from neurologically normal US adults rather than a selected control group. The normative data are standardized for age, sex, and where appropriate education; no standardized normative data for race/ethnicity are available. The use of normative data that do not standardize for race/ethnicity should not affect our results even though there was a relatively increased frequency of black patients in our patient group compared to the US population. Although racial/ethnic differences may affect the results of some cognitive tests, these differences are more highly correlated with education levels than with race/ethnicity alone. Our patients' level of education is greater than the mean for the Oklahoma or US populations and their OPIE-III scores, which predict preillness intellectual level, were also average.

The results of cognitive testing demonstrated that these 24 patients, as a group, performed significantly worse than US population norms on 4 of 11 cognitive domains, even though they had no apparent neurologic deficits and they were performing their normal daily activities with a high level of function. Eighteen (75%) of the patients performed below expectations in at least 1 of these 4 domains. These 4 domains measure cognitive functions such as complex attention and concentration skills, information processing speed (manual dexterity), rapid language generation, and rote memorization (list learning).

The cognitive functions measured by these four domains are among those that are impaired in patients with diffuse, subcortical microvascular lesions[7-9] and could be related to residual effects of diffuse cerebral microvascular thrombosis. Microvascular thrombosis is present in the brain at autopsy in most patients with TTP[22]

and it may be possible that cerebral involvement could also occur among survivors, even without clinical evidence of neurologic involvement during the acute episode. A different pattern of organ involvement occurs in children with HUS. In an autopsy study, microvascular thrombosis was present in the kidneys of all children but no microthrombi were observed in the brain.[22] This is consistent with the absence of cognitive abnormalities in children after recovery from HUS.[23] Although persistent cognitive abnormalities may suggest the possibility of persistent activity of TTP, there were no symptoms or signs of TTP among these 24 patients. All patients had normal histories and physical examinations. No patients had both anemia and thrombocytopenia. The 1 patient with mild anemia and the 1 patient with mild thrombocytopenia had clear alternative etiologies for these abnormalities; their ADAMTS13 activity levels were 80 and 100 percent, respectively. The 11 patients with persistent ADAMTS13 activity of 50 percent or less had normal Hct levels and PLT counts. The 3 patients with persistent ADAMTS13 activity of less than 10 percent have been followed for 4.6 to 10.6 years after their last acute episode of TTP with no evidence of recurrence or persistence of TTP.

A strength of this study was the inclusion of consecutive patients from the Oklahoma Registry with their first episode of TTP and severe ADAMTS13 deficiency. However, this study is preliminary since it has important limitations. The number of patients was small and they represent a small fraction of patients in the Oklahoma Registry. Patients without severe ADAMTS13 deficiency were not studied; therefore, excluding patients with other apparent etiologies who have similar complaints of problems with memory, concentration, and fatigue and similar abnormalities of HRQoL.[6] The small number of patients prevented identification of any patterns between cognitive test results and patients' characteristics or features of the preceding TTP, including age, occurrence of severe neurologic abnormalities, multiple episodes, and interval from an acute episode.

These preliminary observations suggest that TTP may not be an acute, episodic disorder followed by complete recovery. Patients who appear to have a complete recovery from their acute episode of TTP may have persistent neurocognitive abnormalities, causing deficits of attention, processing speed, and memory. These deficits make daily tasks more difficult, resulting in more mistakes and requiring more effort that causes fatigue. Although these abnormalities may not be recognized on routine clinical evaluations, they can be a source of important limitations and frustration for patients. Studies of larger and less selected patient groups will be required to confirm these observations and to determine patient characteristics that may contribute to persistent cognitive abnormalities.

CONFLICT OF INTEREST

The authors have no conflicts of interest with this study.

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