Cognitive functioning in children and adolescents with multiple sclerosis

W.S. MacAllister, PhD; A.L. Belman, MD; M. Milazzo, PNP; D.M. Weisbrot, MD; C. Christodoulou, PhD; W.F. Scherl, MS; T.E. Preston, PhD; C. Cianciulli, PhD; and L.B. Krupp, MD

Abstract—*Objective:* To examine cognitive functioning in children with multiple sclerosis (MS). *Methods:* The authors examined the neuropsychological profile of 37 children with a diagnosis of clinically definite MS and assessed the associations between cognitive function and clinical features. *Results:* Of 37 children and adolescents evaluated, 35% demonstrated significant cognitive impairment. Cognitive functioning was strongly related to several clinical variables, including current Expanded Disability Status Scale, total number of relapses, and total disease length. The consequences of MS adversely affected academic functioning in over a third of the children. *Conclusions:* Cognitive deficits occur in children with multiple sclerosis. Comprehensive treatment planning should involve recognition that they may require academic accommodations for their education.

NEUROLOGY 2005;64:1422–1425

Cognitive deficits occur in approximately 50% of adult patients with multiple sclerosis (MS).[1,2] Domains commonly affected in adults include learning/memory, attention/information processing speed, verbal fluency, executive functions, and visual-spatial skills.[2,3] The cognitive dysfunction may occur early in the disease course[4] and may be among the most troubling disease manifestations.[5]

Cognitive deficits have also been observed in children with MS.[6-8] For example, an evaluation of nine patients with MS between the ages of 10 and 20 years noted that subjects scored significantly below normal range on the Wechsler Intelligence Scale for Children Third Edition (WISC-III) Performance Scale and on the Controlled Oral Word Association (COWA) suggesting that children with MS may have perceptual motor difficulties and attenuated verbal fluency.[8] Prior work has not fully evaluated other specific domains of cognitive function, such as attention and memory, or assessed clinical factors that may predict cognitive decline in children with MS. To address these limitations, we examined 37 consecutive subjects, aged 17 or younger, at the National Pediatric MS Center at Stony Brook, and assessed cognitive, psychosocial, and neurologic functioning.

Methods. *Participants.* This study was approved by the Institutional Review Board for human subject research at the Stony Brook University Hospital. Subjects were recruited from all individuals with MS age 17 years 11 months and younger who were evaluated at the National Pediatric MS Center between October 2001 and August 2004. Written informed consent and assent were obtained.

Eligibility criteria included a diagnosis of childhood MS as jointly confirmed by an adult and pediatric neurologist using McDonald criteria[9] (with the exception that age below 10 years was not an exclusion). Only patients with no other concurrent CNS disorder were included. Only two patients had a preexisting diagnosis of either attention deficit/hyperactivity disorder (ADHD) or a learning disability; these patients were included because it is not known whether these were a separate problem or represent a manifestation of white matter changes prior to the first recognized clinical event. As cognition may be affected by steroids, no patients were evaluated within 30 days of steroid use.

Of 84 individuals who were referred to the National Pediatric MS Center at Stony Brook for evaluation of possible MS, a diagnosis of clinically definite MS was confirmed for 40. Non-MS disorders were diagnosed in 44 children and included acute disseminated encephalomyelitis (n = 14), clinically isolated syndromes (n = 10), and other disorders (n = 16), such as nonspecific white matter changes, migraine, Syndenham's chorea, and somatization disorder. Two of the patients initially identified as having experienced a clinically isolated syndrome went on to have a subsequent relapse, thus qualifying for a diagnosis of MS. As these patients were not considered to have definite MS at the time of the evaluation, they are not included in the present analyses. To date, 37 of the patients with confirmed MS received neuropsychological evaluation and a neurologic evaluation by both of the study neurologists. Demographic and historical data were collected by the study coordinator. All but three patients had normal vision bilaterally. Two patients had unilateral deficits: one had complete loss of vision of one eye (light perception only) and the other had moderate unilateral visual impairment of 20/80 in the right eye. The patient with bilateral visual loss had only mild impairment with visual disturbance of 20/30 in the right eye and 20/40 in the left, which is not of a severity to preclude valid neuropsychological assessment.

Procedure. The patients were evaluated in the General Clinical Research Center of the State University of New York at Stony Brook. Neurologic data collected included current (i.e., measured within 1 week of cognitive evaluation) Expanded Disability Status Scale (EDSS),[10] total number of relapses experienced, age at symptom onset, dichotomously scored (i.e., yes/no) subjective patient report of whether fatigue was problematic, and disease duration

From State University of New York at Stony Brook (Drs. MacAllister, Krupp, Belman, Weisbrot, Christodoulou, and Preston, and M. Milazzo and W.F. Scherl); St. Charles Rehabilitation Hospital (Dr. Preston), Long Island, NY; and Weldon Rehabilitation Hospital-Mercy Medical Center (Dr. Cianciulli), Springfield, MA.

Supported in part by National MS Society Pilot Grant PP 0773 and the National Center for Research Resources (Grant # M01-RR10710).

Received July 14, 2004. Accepted in final form January 3, 2005.

Address correspondence and reprint requests to Dr. Lauren B. Krupp, State University of New York at Stony Brook, HSC T-12 020, Department of Neurology, Stony Brook, NY 11794-8121; e-mail: lkrupp@notes.cc.sunysb.edu

in whole months elapsed from symptom onset to time of cognitive evaluation.

Cognitive evaluation. The participants received a brief standardized neuropsychological battery designed to assess all relevant cognitive domains. Although a global measure of cognitive function (i.e., IQ) may have provided interesting information, time constraints precluded inclusion of such instruments and, as declines on the WISC-III have been documented elsewhere,[8] it was deemed more important to assess specific cognitive domains, including attention, language, memory, visual-spatial, and motor functions. The test battery included six tests. The Trailmaking Test[11] is a multifactorial task that is divided into two parts. Part A requires rapid visual scanning and motor speed, whereas Part B requires these skills as well complex attentional functions. The COWA[12] is a test of verbal fluency where the subject is asked to list words that begin with a target letter. The Boston Naming Test[13] is a test of naming ability. To assess receptive language functions, the Listening to Paragraphs subtest of the Clinical Evaluation of Language Fundamentals–III[14] was administered. With respect to memory, two subtests of the Wide Range Assessment of Memory and Learning were utilized: Verbal Learning and Visual Learning.[15] Both immediate and delayed recall were assessed. Finally, the Beery Test of Visual Motor Integration[16] provided an evaluation of graphomotor construction.

The battery required approximately 2 hours depending on the patient's ability and was administered by a neuropsychologist in a single session. Breaks were provided when requested by the patient or if fatigue was evident. Performances were considered impaired when scores fell 1.5 SDs or more below the mean in comparison to published normative data. The cutpoint of 1.5 SDs was chosen as this is considered a deficient score by most neuropsychologists. As normative data are not available for the Boston Naming Test for children over 13,[17] older children were compared to norms for 13-year-olds, likely resulting in a conservative estimate of their functioning in this domain. A patient was considered to have overall cognitive impairment if scores fell 1.5 SDs or more below published norms on at least two cognitive tasks (a criterion considered to be unlikely to be due to chance).[18] All raw scores were converted into z-scores for subsequent correlational analyses to control for the effect of age and differing (i.e., age-appropriate) test forms. To represent overall cognitive functioning, a neuropsychological composite score was generated by calculating the mean of all test z-scores. Additionally, patients were administered the 9-hole Peg Test from the MS Functional Composite[19] to adjust for fine motor functioning that may affect cognitive tests that require motor responses. One-year follow-up neuropsychological data were available for eight patients, and these data continue to be collected.

Psychological function. A subset of the population (n = 13) was formally assessed for affective disorders by a psychiatrist utilizing the Schedule for Affective Disorders and Schizophrenia for School Aged Children.[20] The patients were not preselected for the evaluation, but rather were seen subsequent to the availability of the psychiatrist on the day of their study visit. Information regarding special educational services provided at school was also collected.

Statistical analyses. Pearson correlations were used to assess the interrelations of clinical variables and the neuropsychological composite score. A point biserial correlation was used to assess the relations between reported fatigue and cognitive function. Partial correlations were also conducted to control for the effects of dominant hand motor function. For the purpose of this exploratory study, a significance value of $p < 0.05$ was used throughout, although, despite the relatively small sample size, some reached significance at more stringent levels (e.g., $p < 0.01$). All analyses were performed with Statistical Package for the Social Sciences 11.5 software.

Results. *Demographic and neurologic data.* Patient characteristics and clinical data at the time of the neuropsychological evaluation are presented in table 1. The majority of patients had symptom onset and diagnosis during the teenage years. All but one patient presented with a relapsing remitting course. Fatigue was a concern for nearly half of the sample (48.6%). Most patients were on disease modifying therapy at the time of the evaluation; three were on combination therapies.

Table 1 *Patient characteristics (n = 37)*

Current age, y, mean/median (SD, range)	14.86/16 (2.15, 8–17)
Mean/median age at symptom onset, y (SD, range)	13.51/14 (2.56, 4–17)
MS type, n	
Relapsing-remitting	36
Primary progressive	1
Mean/median number of relapses (SD, range)	3.16/2 (2.37, 1–13)
Current EDSS, mean/median (SD, range)	1.50/1 (1.28, 0–4)
Current fatigue, n (%)	18 (48.6)
Mean/median months since symptom onset (SD, range)	19.73/16 (18.43, 1–75)
Cognitive impairment, n (%)	13/37 (35.1)
Patients requiring academic assistance in school, n (%)	13/37 (35.1)
Mood disturbance (of those receiving formal psychiatric evaluation), n (%)	6/13 (46.1)
Interferon β-1-a IM, n (%)	13 (35.1)
Interferon β-1-a subcutaneous, n (%)	4 (10.8)
Interferon β-1-b, n (%)	7 (18.9)
Glatiramer acetate, n (%)	6 (16.2)
Combination therapy, n (%)	
Interferon β-1-a subcutaneous/ mitoxantrone	1 (2.7)
Interferon β-1-b/mitoxantrone	2 (5.4)

MS = multiple sclerosis; EDSS = Expanded Disability Status Scale.

Neuropsychological performance. This group of children with MS showed a range of cognitive deficits. A total of 35.1% (13/37) of the patients showed major cognitive impairment, defined by impaired performance on at least two cognitive tasks. A total of 59% (22/37) had an impaired performance on at least one neuropsychological test. Interestingly, neither the patient with a preexisting diagnosis of ADHD nor the patient with a preexisting learning disability showed objective cognitive impairment on the neuropsychological battery.

The most common impairment was in complex attention (e.g., rapidly shifting attention between competing stimuli), affecting 29.7% of patients (11/37). Language was deficient for many, with 18.9% showing impairment in naming (7/37), and 13.5% showing poor receptive language (5/37). Verbal fluency was intact for all of the patients. Immediate verbal memory was impaired for only 1 patient (2.7%), whereas delayed recall was deficient in 7 patients (18.9%). Immediate recall of visual information was impaired for 3 patients (8.1%) and 4 (11%) demonstrated visual memory impairment after a delay. Thus, both encoding problems and forgetting are suggested. Visual-spatial functions were impaired in 2 patients (5.4%).

Psychological functioning. Six of the 13 patients who underwent a structured psychiatric evaluation received a formal diagnosis of an affective disorder. Specifically, two patients were diagnosed with both a major depressive dis-

Table 2 *Intercorrelations of clinical factors and cognition*

	Cognition composite	Partial correlations controlling for dominant hand fine motor function
EDSS	$r = -0.574$*	pr = −0.452†
	$p = 0.000$	$p = 0.006$
Total relapses	$r = -0.526$*	pr = −0.336†
	$p = 0.001$	$p = 0.045$
Age at onset	$r = 0.330$†	pr = 0.103
	$p = 0.046$	$p = 0.551$
Fatigue	$r = -0.233$	pr = −0.277
	$p = 0.165$	$p = 0.102$
Disease length	$r = -0.410$*	pr = −0.314
	$p = 0.012$	$p = 0.062$

* $p < 0.01$.
† $p < 0.05$.

EDSS = Expanded Disability Status Scale.

order and anxiety disorder–not otherwise specified (NOS); two patients were diagnosed with a major depressive disorder; one had an anxiety disorder NOS; and one had panic disorder and a generalized anxiety disorder.

Correlations between neurologic factors and cognition. As shown in table 2, there were clear relations between neurologic factors and cognitive performance. Current EDSS score accounted for almost 33% of the variance in cognition. The total number of relapses experienced accounted for about 28% of the variance in cognition and total disease length accounted for nearly 17% of the variance. Age at disease onset was also significantly related to cognitive dysfunction. However, as age at onset and total disease length share considerable variance, this should be interpreted with caution. When multiple regression assessed the relative contributions of these factors to cognition, disease length emerged as the more salient predictor (pr = −0.288, $p = 0.089$) and age at onset no longer accounted for much variance (pr = 0.132, $p = 0.442$).

After controlling for dominant hand fine motor functioning, the relations of both EDSS and number of relapses with cognition remained significant. Though the correlation between disease length and cognitive function was no longer significant after controlling for motor function, a trend was evident. Subjective report of fatigue did not significantly correlate with cognition.

A hierarchical multiple regression assessing the relative contribution of the clinical variables in predicting cognition while controlling for dominant hand manual dexterity showed that EDSS was the strongest predictor (pr = −0.452, $p = 0.006$). Number of relapses was the second strongest predictor (pr = −0.336, $p = 0.045$) and the other variables did not add any additional significant predictive power.

Academic consequences. For the 22 children for whom data were available, the average number of school days missed due to MS was 24.73, ranging from 0 to 225. Three of the patients required homeschooling. A total of 13 of 37 patients (35.1%) required some type of assistance or change in their school curriculum as a result of cognitive dysfunction. As an example, one patient was unable to memorize her locker combination at school, which led to her being continually late to a class and failing the course. This difficulty was obviated by providing her with a lock and key, rather than a traditional combination lock. She also required increased time to complete her examinations. Other children reported difficulty maintaining focus at school due to attention deficits. Many of these cognitively impaired children required academic accommodations at school to aid them in their studies. In the majority of cases, such accommodations have been adequate to overcome most of their cognitive limitations.

For some of the children, however, the effect of MS on academic performance was severe. For example, one 13-year-old girl had been under consideration for the gifted program prior to developing MS. Following onset of MS and subsequent acquired cognitive deficits, she required remedial classes after only 1 year of disease duration.

Two girls dropped out of school. One patient dropped out of a community college due to multiple hospitalizations for frequent relapses, cognitive deficits, and inability to handle the workload. As her disease course stabilized she was able to return to school. The other patient permanently dropped out of high school due to severe depression. Two boys, one in elementary school and the other in high school, repeated a year in school due to cognitive difficulty and multiple missed school days.

One year follow-up. Of the 37 children who were initially evaluated for this study, eight have received 1-year follow-up neuropsychological re-evaluations. Three of the eight were cognitively impaired at baseline and all three went on to decline further. Among the five children who were cognitively intact at baseline, two declined at follow-up. During the interim period, both of these boys experienced relapses; one had five more relapses and the other had three. At follow-up, one manifested impairment across numerous domains, including attention, memory, language, visual-spatial functions, and motor functions. The other now demonstrated mild word finding deficits and verbal memory problems.

Discussion. Cognitive impairment may occur in children and adolescents with MS, a finding consistent with prior studies of MS in children.[6-8] In the present study, over a third of the patients showed deficits. As in adult MS groups, attention and memory were among the most frequent problems.[2] In contrast, however, visual spatial functions were less frequently affected and verbal fluency was unaffected. Further, confrontation naming was frequently impaired in these children, a function that is typically intact in adults with MS.[2]

Strong correlations were present between cognition and EDSS, number of relapses, and the total disease duration. In contrast, in adult MS there have not been strong relations between these variables and cognitive function, and the relations between EDSS and cognition have been weak or inconclusive.[21-23] Nonetheless, similar to findings in adult MS, cognitive deficits were seen in some children in the absence of major physical dysfunction.

Affective disorders were diagnosed in nearly half of the patients who received a psychiatric evaluation.

Furthermore, many children experienced major problems in school due to cognitive deficits and the overall impact of the disease. Since the most cognitively impaired children had high rates of hospitalization, it is not possible to distinguish the relative contributions of different disease factors to academic problems.

To date there have been no systematic prospective longitudinal studies of children with MS. While our sample is small, the follow-up assessment of eight patients showed that children with MS can show cognitive decline over a 1- to 2-year period. Five showed progressive cognitive decline, which included all three children who were impaired at baseline and two children who had been without cognitive deficits.

This study was limited by lack of an age- and demographic-matched control group. This restricts the generalizability of the conclusions. However, normative comparisons provide important information that is meaningful from a clinical perspective. Another limitation was the fact that not all patients received a psychiatric evaluation. Future studies should include psychiatric assessment on all patients.

References

1. Peyser JM, Rao SM, LaRocca NG, Kaplan E. Guidelines for neuropsychological research in multiple sclerosis. Arch Neurol 1990;47:94–97.
2. Rao SM, Leo GJ, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. Neurology 1991;41:685–691.
3. Benedict RH, Fischer JS, Archibald CJ, et al. Minimal neuropsychological assessment of MS patients: a consensus approach. Clin Neuropsychol 2002;16:381–397.
4. Lyon-Caen O, Jouvent R, Hauser S, et al. Cognitive function in recent-onset demyelinating diseases. Arch Neurol 1986;43:1138–1141.
5. Rao SM, Leo GJ, Ellington L, Nauertz T, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis. II. Impact on employment and social functioning. Neurology 1991;41:692–696.
6. Bye AM, Kendall B, Wilson J. Multiple sclerosis in childhood: a new look. Dev Med Child Neurol 1985;27:215–222.
7. Dale RC, de Sousa C, Chong WK, Cox TCS, Harding B, Neville BGR. Acute disseminated encephalomyelitis, multiphasic disseminated encephalomyelitis and multiple sclerosis in children. Brain 2000;123:2407–2422.
8. Kalb RC, DiLorenzo TA, LaRocca NA, et al. The Impact of early onset mutliple sclerosis on cognitive and social indices. Int J MSCare [serial online]. Sept 1999;1:1–6. Available at: http://mscare.com. Accessed December 15, 2004.
9. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the Diagnosis of Multiple Sclerosis. Ann Neurol 2001;50:121–127.
10. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983;33:1444–1452.
11. Army individual test battery: manual of direction and scoring. Washington, DC: War Department, Adjutant General's Office, 1944.
12. Rao SM, Cognitive Function Study Group of the National Multiple Sclerosis Society. A manual for the brief, repeatable battery of neuropsychological tests in multiple sclerosis. Milwaukee, WI: Section of Neuropsychology, Medical College of Wisconsin, 1990.
13. Kaplan EF, Goodglass H, Weintraub S. The Boston Naming Test (2nd ed.). Philadelphia: Lea & Febiger, 1983.
14. Semel E, Wiig EH, Secord WA. Clinical evaluation of language fundamentals. 3rd ed. NY: Psychological Corporation, 1995.
15. Sheslow D, Adams W. WRAML: Wide Range Assessment of Memory and Learning. 1990.
16. Beery KE. The Visual-Motor Integration Test (4th ed.). Administration, scoring, and teaching manual. 4th ed. Cleveland: Modern Curriculum Press, 1997.
17. Spreen O, Strauss E. A compendium of neuropsychological tests: administration, norms, and commentary. New York: Oxford University Press, 1998.
18. Ingraham LJ, Aiken CB. An empirical approach to determining criteria for abnormality in test batteries with multiple measures. Neuropsychology 1996;10:120–124.
19. Fischer JS, Jak AJ, Knicker JE, Rudick RA, Cutter G. Administration and scoring manual for the Multiple Sclerosis Functional Composite measure (MSFC). Canada: Demos, 1999.
20. Kaufman J, Birmaher B, Brent D, et al. Schedule for affective disorders and schizophrenia for school-age children—present and lifetime version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 1997;36:980–988.
21. Rao SM, Leo GJ, Aubin-Faubert P. On the nature of memory disturbance in multiple sclerosis. J Clin Exp Neuropsychol 1989;11:699–712.
22. Beatty WW, Goodkin D, Hertsgaard D. Clinical and demographic predictors of cognitive performance in multiple sclerosis. Arch Neurol 1990;47:305–308.
23. Rao SM, Leo GJ, Haughton VM, Aubin-Faubert P, Bernardin L. Correlation of magnetic resonance imaging with neuropsychological testing in multiple sclerosis. Neurology 1989;39:161–166.