Neurocognitive Development of Children After a Cerebellar Tumor in Infancy: A Longitudinal Study

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Purpose: **To assess the long-term neuropsychologic effects experienced by children who have tumors in the cerebellum that are diagnosed and treated during infancy.**

Patients and Methods: **Twenty-seven children with posterior fossa tumors diagnosed at less than 36 months of age were assessed prospectively with a comprehensive set of age-appropriate tests. Group means and SDs are reported for assessments conducted at diagnosis (analysis 1) and at the most recent follow-up appointment (analysis 2). Cognitive developmental growth curves were derived from the prospective data (analysis 3) using mixed model regression analyses and controlling for age at diagnosis and socioeconomic status.**

Results: **In the first analysis, eight of 11 infants at diagnosis scored within normal limits on all neuropsychologic domains, except for motor skills, which were impaired. In the second analysis, mean scores at the most recent follow-up of 21 of 27 patients were mostly in the normal range; however, group comparisons between those who had (n = 7) and had not (n = 14) been treated with cranial radiation therapy (CRT) showed that patients in the irradiated (CRT) group scored significantly lower than those in the nonirradiated (No-CRT) group on verbal intelligence quotient (IQ) and in the motor domain. In the third analysis (growth curves of CRT and No-CRT groups), statistically significant differences in slope were found on verbal IQ, performance IQ, perceptual-motor skills, language, and attention/executive skills. Slopes on the fine-motor domain were similar; both groups declined at approximately the same rate.**

Conclusion: **Neurocognitive development and outcome of children with cerebellar tumors diagnosed in infancy is very positive among those who were treated with surgery and chemotherapy. Declines in performance across time were minimal, and scores tended to remain within normal limits. By itself, a cerebellar tumor in infancy does not seem to have a significant impact on children. However, those who received CRT as part of their treatment are likely to have neurocognitive and psychosocial deficits that require remediational interventions.**

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THE INCIDENCE OF CNS tumors in the United States has surpassed acute lymphocytic leukemia to become the most common type of cancer occurring in children younger than 15 years of age.[1,2] Sixty percent of such tumors in childhood occur in the posterior fossa. Patients with tumors in this location are considered to be at risk for neuropsychologic sequelae[3]; hence such tumors have been the subject of research for neuropsychologic effects more so than those in any other brain location group.[4-27] Most of the studies are retrospective in design and are very limited in the use of standardized assessments; nevertheless, their results indicate that certain variables contribute to increased risk of neuropsychologic impairments; namely, younger age at diagnosis[6,9,12,14,16,22-24,27-29] and treatment with cranial radiation therapy (CRT).[7-11,14-16,22-28,30-32] Specific location within the cerebellum has been discussed as well,[9,11,14-16] along with time since treatment.[8,15,22,27,28]

Little is known about the long-term effects of brain tumors on children, particularly those with tumors that appear in the cerebellum during infancy. Packer et al[21] found that children with posterior fossa tumors who did not receive CRT or methotrexate had fewer deficits than those who had received CRT. However, two other studies demonstrated that children with tumors in the posterior fossa had cognitive deficits even when they did not receive CRT,[17,19] supporting the notion that the cerebellum is involved in higher-order cognitive skills, not just motor coordination. Courchesne et al[33,34] compared the performance of autistic children with that of children with cerebellar lesions on a voluntary, non–motor-shifting attention task and found that the performance of both groups was similarly impaired, compared with that of normal controls.

This prospective study was conducted to assess the long-term neuropsychologic effects experienced by children who have tumors in the cerebellum that are diagnosed and treated during infancy. We considered (1) the effects of the tumor itself on 11 patients who had been assessed at

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diagnosis; (2) late effects at the most recent assessment of 21 patients; and (3) change over time among 15 patients who had been assessed at least two times, controlling for sex, race, and socioeconomic status (SES). In the latter analysis, patients who had not received CRT were compared with those who had been treated with CRT.

We hypothesized that (1) infants with cerebellar tumors would show neuropsychologic deficits at diagnosis; (2) impairment at long-term follow-up would be related to treatment effects, specifically CRT; and (3) neuropsychologic performance would decline as time from diagnosis increased. These hypotheses were tested with three analyses: (1) neuropsychologic performance of infants at diagnosis; (2) neuropsychologic performance of patients tested from 1 to 13 years after diagnosis; and (3) development of neuropsychologic skills across time.

PATIENTS AND METHODS

Patients

As part of a larger study (360 patients) conducted between 1983 and 1997 that assessed the neuropsychologic status of children with brain tumors, we conducted serial evaluations of 27 children with posterior fossa tumors that were diagnosed when they were less than 36 months of age. All children in this age group who had been evaluated are included in this report. This represents more than 90% of the children treated at our institution who met study criteria (children with cerebellar tumors diagnosed at $<$ 36 months of age). Table 1 lists the demographic and medical characteristics of the sample, which included 12 female and 15 male patients. Most (18 patients) were white, and the rest were of Hispanic (seven) or African-American (two) origin. Mean age at diagnosis was 22 months (range, 7 to 35 months). Almost equal numbers of patients (four or five) were represented in each level of socioeconomic class (I to V), except for four patients for whom SES was unknown.[35]

Diagnoses included medulloblastoma (15 patients), astrocytoma (seven patients), ependymoma (three patients), astrocytoma-ependymoma (one patient), and dermoid cysts (one patient). Most tumors (15) involved the midline of the cerebellum. Nine of these extended into the fourth ventricle, with one extending into the right hemisphere of the cerebellum as well. In two cases, the tumor was only in the fourth ventricle. Three tumors were in the right hemisphere of the cerebellum, and three were in the left hemisphere. One of the right hemisphere tumors also extended into the brainstem. Location was undetermined in four patients whose records were incomplete.

All patients had surgery to remove the tumor. Twenty had complete resection, and seven had partial resection. Most (21 patients) experienced increased intracranial pressure; therefore, 19 patients had shunts installed. Twenty had been treated with various combinations of chemotherapy, but most had received nitrogen mustard, vincristine, procarbazine, and prednisone (MOPP) or MOPP with methotrexate added (dose of methotrexate was 6 g/m^2 administered intravenously.) Seventeen had received corticosteroids, and six had been given an anticonvulsant (usually phenytoin). Seven had received radiation to the brain at least 6 months before the last neuropsychologic examination. Each of these had whole-brain radiation (dosage, 30 to 40 Gy) and radiation to the cerebellum (total dosage, 40 to 50 Gy). Three had radiation to the spine as well (30 to 45 Gy). Twelve patients had at least one tumor recurrence between the time of diagnosis of the original tumor and the most recent neuropsychologic assessment. At the time of data analysis, 17 (63%) were surviving and 10 (37%) had died. The survival rate was 71% for patients in both the irradiated and nonirradiated groups.

Table 1. Demographic and Medical Characteristics of Total Sample (n = 27)

Characteristic		No. of Patients
Sex		
Male		15
Female		12
Ethnicity		
White		18
Other		9
Socioeconomic class		
I, highest		4
II		5
III		4
IV		5
V, lowest		5
Unknown		4
Age at diagnosis, months		
Mean	22	
Range	7-35	
Diagnosis		
Medulloblastoma		15
Astrocytoma		7
Ependymoma		3
Astrocytoma-ependymoma		1
Dermoid cysts		1
Tumor locations		
Midline and/or fourth ventricle		17
Right cerebellum		3
Left cerebellum		3
Unknown		4
Treatment		
Surgery		27
Partial resection		7
Total resection		20
CRT, whole brain (30-40 Gy) + cerebellum (40-50 Gy)		7*
Chemotherapy		20
MOPP and/or M-MOPP		17†
Other		3‡
Shunt		19
Hydrocephalus		21
Corticosteroids		17
Anticonvulsants		6
Tumor activity		
Progression/recurrence		12
Patient status		
Surviving		17
Deceased		10

Abbreviation: M-MOPP, MOPP with methotrexate added.
*Three of the seven patients also received 30 to 45 Gy to the spine.
†Three of the 17 patients received MOPP plus cisplatin.
‡One patient received cisplatin alone, and two received other chemotherapy.

Table 2 shows the neuropsychologic test sequences across time for each subject. Eleven had been assessed for the first time during the year of diagnosis, most within 4 months (Table 2, boxed x), and these results

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Table 2. Test Schedules of Subjects

		Test Intervals (at diagnosis and years post diagnosis)												
Subject		Dx	1	2	3	4	5	6	7	8	9	10	11	12	13
1		⊠													
2		⊠													
3		⊠													
4		⊠													
5		⊠													
6		⊠	⊠												
7	→	⊠	⊠												
8	→	⊠	×		⊠										
9	→	⊠	×	×	×		×		×	⊠					
10	→	⊠	×	×	×	×	⊠								
11	→	⊠		×	×	×	×		×	×	⊠				
12			×												
13			×	⊠											
14				×		⊠									
15	→		×	×	×	×	×	×	×	×	⊠				
16	→			×	×	⊠									
17	→				×			×			⊠				
18	→				×	×	×	×	×	×	×	×	⊠		
19						⊠									
20	→					×			⊠						
21	→					×	×	×	×	×	⊠				
22	→						×	×	⊠						
23	→					×					×		⊠		
24	→						×	×	×	×	×	×	×		⊠
25	→								×		×			⊠	
26										⊠					
27													⊠		
		Dx	1	2	3	4	5	6	7	8	9	10	11	12	13

Total Sample Includes Ss 1-27. Medical, demographic characteristics, Tables 1,2.
Analysis 1 ⊠ Includes Ss 1-11. Descriptive statistics. Acute effects. Patients assessed at diagnosis.
Analysis 2 ⊠ Includes Ss 6-11, 13-27. Descriptive statistics. Late effects. Patients' last follow-up (if > 1 yr post diagnosis). Tables 4,5.
Analysis 3 → Includes Ss 7-11, 15-18, 20-25. Individual growth curve analysis. Developmental effects. Patients with ≥ 2 assessments. Figures 1,2.

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were used to test for acute effects of the tumor (analysis 1). Follow-up assessments occurred at varying times after that, up to 13 years from diagnosis.

Twenty-one patients had follow-up assessments and/or had been tested for the first time more than 1 year after diagnosis (Table 2, shaded x). The results of their most recent examination were used to test for long-term effects of the tumor and treatment (analysis 2). (Note: Patients with assessments beginning later than 1 year after diagnosis were referred to the institution after receiving initial treatment elsewhere.)

Fifteen patients included in the prospective study had had at least two assessments, but most (13 patients) had been assessed at least three times (Table 2, boxed arrow). Growth-curve analyses were conducted to assess the developmental effects of tumor and treatment across time (analysis 3). One of the advantages of growth-curve analyses is that consistent timing of the assessments across subjects is not required.

Procedures

After approval of the study by the institution's internal review board and before the first assessment, informed consent was obtained from each parent in addition to assent from each child who was age 7 or older. The study was described verbally, and parents were given a copy of the consent form, which contained a written description.

Table 3 lists the neuropsychologic tests and composition of the cognitive domains used in the study.[36-52] Most of the infants whom we were able to assess at the time of diagnosis were assessed using the Bayley Scales of Infant Development[36] (two were administered the Stanford-Binet, 4th edition[38]). This assessment allowed us to estimate the effects of the tumor itself in infants before treatment.

Table 3. Neuropsychologic Domains and Tests of Measurement

Intelligence
Bayley Scales of Infant Development,[36] ages 1 to 42 months
McCarthy Scales of Children's Abilities,[37] ages 3 to 5 years
Stanford-Binet Intelligence Scale, 4th edition,[38] ages 2 to 16+ years
Wechsler Intelligence Scale for Children, revised,[39] ages 6 to 15 years
Wechsler Adult Intelligence Scale,[40] ages 16+ years
Academic achievement
Wide Range Achievement Test (spelling, arithmetic),[41] ages 5 to 16+ years
Peabody Individual Achievement Test (reading recognition, reading comprehension),[42] ages 5 to 16+ years
Language
Wechsler Subtests: Information, Similarities, Comprehension[39,40]
Peabody Picture Vocabulary Test, revised,[43] ages 3 to 16+ years
Word Fluency (F, A, S),[44] ages 5 to 16+ years
Memory
Verbal Selective Reminding Test,[45] ages 5 to 16+ years
Nonverbal Selective Reminding Test,[46] ages 5 to 16+ years
Attention/executive functions
Freedom From Distractibility Deviation Quotient,[47] ages 6 to 16+ years
Trail Making B,[48] ages 5 to 16+ years
Fine motor
Finger tapping,[48] ages 5 to 16+ years
Grooved Pegboard,[49] ages 5 to 16+ years
Trail Making A,[48] ages 5 to 16+ years
Perceptual-motor
Beery Visual-Motor Integration Test,[50] ages 3 to 16+ years
Wechsler Subtest: Block Design[39,40]
Tactile-spatial
Tactile Form Perception Test,[51] ages 5 to 16+ years
Psychosocial
Child Behavior Checklist,[52] ages 4 to 16 years

In follow-up examinations of these patients and the remainder of the sample, age-appropriate neurocognitive tests were administered.[36-40] Although the use of different levels and types of tests is not ideal, it is unavoidable in prospective studies of infants and children that are conducted over an extended period of time. To reduce practice effects, alternative forms of the tests were used when available (eg, Peabody Picture Vocabulary Test,[43] Wide Range Achievement Test,[41] and Selective Reminding Tests[44,45]).

National samples provided scores from which the norms (means and SDs) for the intelligence and academic achievement tests were derived; these were standardized to a mean of 100 and an SD of 15. To achieve comparability across intelligence measures, McCarthy and Stanford-Binet summary scores were converted to the same scale as the Wechsler Intelligence Scale for Children–Revised. Other neuropsychologic variables were standardized using available age norms to a mean of 10 and an SD of 3. Scores on timed measures were transformed so that a higher score was better, which made them consistent with all other measures.

For statistical analysis, test variables were grouped into ability domains on the basis of intercorrelations among variables and/or results from previous research. This data-reduction strategy reduced the overall number of statistical comparisons and thus minimized inferential errors associated with multiple univariate tests of dependent variables.[53] Test scores within a domain were standardized and averaged to obtain a domain score. Because of small sample sizes in some SES levels, SES levels 1, 2, and 3 were grouped together (high SES), and levels 4 and 5 were grouped together (low SES). Ethnicity was categorized as white or nonwhite.

Statistical Design

Descriptive statistics were obtained for the performance of 11 patients in the sample of 27 who were assessed soon after diagnosis (analysis 1). This was to estimate the acute effects of the tumor before the onset of treatment effects. Descriptive statistics were also obtained for the 21 patients whose most recent assessment was more than 1 year after diagnosis (analysis 2). This retrospective analysis was designed to estimate the long-term effects of the tumor and its treatment.

For the prospective analysis (analysis 3), individual growth-curve analyses were conducted on 15 children who had been assessed at least two times (range, two to nine examinations; 13 had $\geq$ three examinations). We excluded six children who had been assessed only with the Bayley Scales and no other test. The method used for the growth-curve analyses was mixed model regression analyses, using PROC MIXED in SAS (SAS, Cary, NC). Growth curves for patients were averaged, and comparisons were made between those who received CRT and those who did not, controlling for SES and age at diagnosis. In this analysis, we tried a number of different variations of model-fitting, ie, analyses restricted first to subjects with at least three observations, and then two observations; compound symmetry versus auto-regressive covariance matrices; and random coefficients models. These comparative analyses yielded similar results.

RESULTS

Early Effects (Analysis 1)

Among the 11 infants whom we were able to assess at the time of diagnosis, eight scored within normal limits on the Bayley Scales of Mental Development[36] or the Stanford-

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Binet[38] (mean, 91.8; SD, 24.5), although three had significant impairments. Five infants scored one SD below the normal mean on the Bayley Scale of Motor Development[36] (mean, 75.6; SD, 12.8), and five were so impaired that they could not be tested on the motor scales. In sum, most of the impairments at diagnosis were in the motor domain of functioning.

Late Effects (Analysis 2)

Twenty-one of the 27 patients had follow-up assessments and/or had been tested for the first time more than 1 year after diagnosis. Their ages at this assessment ranged from 3 to 14 years (mean,9 years), and time since diagnosis was 2 to 13 years (mean, 7 years). Four patients were still younger than 5 years old, and 17 were older than 5 years. One third of these patients had received CRT, so the sample was divided into CRT and No-CRT groups, and their respective group performances were compared. Table 4 provides a description of patient demographic and medical characteristics for these groups.

Mean scores for all patients at this assessment (most recent) were in the normal range for the most part, albeit on the lower end of normal (Table 5). Verbal intelligence quotient (IQ) was 87, and performance IQ was almost 87. The patients were doing well academically, with a mean score of 90, and language and attention skills were intact (mean scores of 8). Verbal memory was better preserved than spatial memory and perceptual-motor skills. The latter two skills were in the impaired range (mean score < 7). Motor scores were variable, as shown by a higher SD, but the mean was still within normal limits (7.5).

Table 4. Demographic and Medical Characteristics of CRT and No-CRT Groups at Last Follow-up

Characteristic	CRT (n = 7)	No-CRT (n = 14)
Sex		
Male, n	3	10
Female, n	4	4
Mean SES level	2.71	3.38
Mean test age, years	10.7	8.5
Mean years from diagnosis	8.7	6.1
Tumor type		
Medulloblastoma, n	3	8
Astrocytoma, n	3	3
Ependymoma, n	1	1
Astrocytoma/ependymoma, n		1
Dermoid cyst, n		1
Chemotherapy, n	6	12
Disease recurrence, n	6	5
Survival		
n	5	10
%	71	71

Table 5. Mean Scores of CRT and No-CRT Groups at Last Follow-up

	Irradiated (n = 7)		Nonirradiated (n = 14)		Total Sample (n = 21)	
Neuropsychology Domain	Mean	SD	Mean	SD	Mean	SD
Verbal IQ*	76.86	17.7	99.23	11.5	87.02	2.0
Performance IQ	80.14	11.0	94.54	23.5	86.62	2.2
Academic	86.75	13.9	92.46	11.8	90.41	2.2
Language	6.8	3.3	8.9	1.5	8.1	2.4
Attention/executive	6.2	3.3	9.4	3.1	8.0	3.4
Memory	6.8	3.5	7.5	3.6	7.3	3.4
Verbal memory	9.0	2.6	7.0	4.2	7.7	3.8
Spatial memory	4.3	5.1	7.7	4.6	6.9	4.7
Perceptual-motor	5.2	1.9	7.7	3.0	6.8	2.9
Motor†	4.4	1.0	9.1	3.8	7.5	4.1

NOTE. For verbal IQ, performance IQ, and academic domains, normal range is 85 to 115 (mean, 100; SD, 15). For all other measures, normal range is 7 to 13 (mean, 10; SD, 3).

*Between group differences ($P < .003$).

†Between group differences ($P < .016$).

However, when the sample was divided between those who had received cranial irradiation (n = 14) and those who had not (n = 7), there was a sharp contrast between the mean scores of each group on most neurocognitive domains (Table 5). Patients in the irradiated group almost consistently scored in the impaired range, whereas mean scores of patients in the nonirradiated group were within normal limits. There were statistically significant differences between groups on verbal IQ ($t = 3.44$; $P < .003$) and the motor domain ($t = 2.4$; $P < .016$). Despite the contrast in scores between the two groups, differences on other measures did not meet statistical significance because of small numbers.

Results of the Child Behavior Checklist[52] administered to 19 participants at this last follow-up were similar to those found on the neurocognitive measures with respect to the total sample and irradiated versus nonirradiated groups. That is, mean scores on the social competence, behavior problems, and internalizing/externalizing scales were within normal limits (based on girls/boys nonclinical norms for 6- to 11-year-olds). However, dividing the sample between irradiated and nonirradiated patients showed that the means for the five irradiated subjects were at least one SD below the normal mean on activities, social, school, social competency, total behavior problems, internalizing, and externalizing scales. The nonirradiated subjects' mean scores were within normal limits, except on the social scale, which was one SD below the normal mean.

Correlations were not significant between any of the neuropsychologic domains or behavioral scales and the following variables: time since diagnosis, tumor recurrence, surgery type (partial versus total), site of tumor (cerebellar midline versus cerebellar hemisphere), or life status (surviving versus deceased).

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Developmental Change (Analysis 3)

Initial growth-curve analyses suggested that the shapes of the growth curves were generally similar between male and female patients, but there were some differences between high and low socioeconomic groups and ethnic groups, with whites and higher socioeconomic groups obtaining better scores. In view of ours and others' research suggesting that age at diagnosis, SES, and CRT are significant predictors of neuropsychologic performance, we conducted growth-curve analyses comparing the performance of those treated with and without CRT, controlling for SES and age at diagnosis. (Because ethnic group and SES were confounded—whites comprised most of the higher SES groups and nonwhites the lower SES groups—we controlled only for SES and not ethnicity.)

Figures 1 and 2 illustrate the observed means and model-derived average slopes of the growth curves for the CRT and No-CRT groups on each neurocognitive domain. The two groups were compared only on differences in developmental slope by modeling interaction terms between group and time since diagnosis. The predicted values at either end of the distribution of time since diagnosis, particularly those for later follow-up, are not very stable. The first *P* value shown refers to the analyses without covariates, and the *P* value in parentheses indicates the analyses in which SES and age at diagnosis were included in the model.

Figure 1A shows that patients in the irradiated group continued to decline across time on verbal IQ, whereas patients in the nonirradiated group tended to stay on course with developmental norms. Differences in slope were significant ($P < .001$). On performance IQ (Fig 1B), there was less of a difference between the two groups, but results were still significant ($P < .05$). A similar result was found for the academic domain (Fig 1C). Differences were significant at the .05 level.

On the perceptual-motor domain (Fig 1D), differences were significant ($P < .05$), with scores of patients in the irradiated group declining to a level well below the normal range. Interestingly, on the motor domain (Fig 1E), the groups were not significantly different, although the scores of patients in the irradiated group did fall to the impaired range, whereas the performance of patients in the nonirradiated group remained within the normal limits.

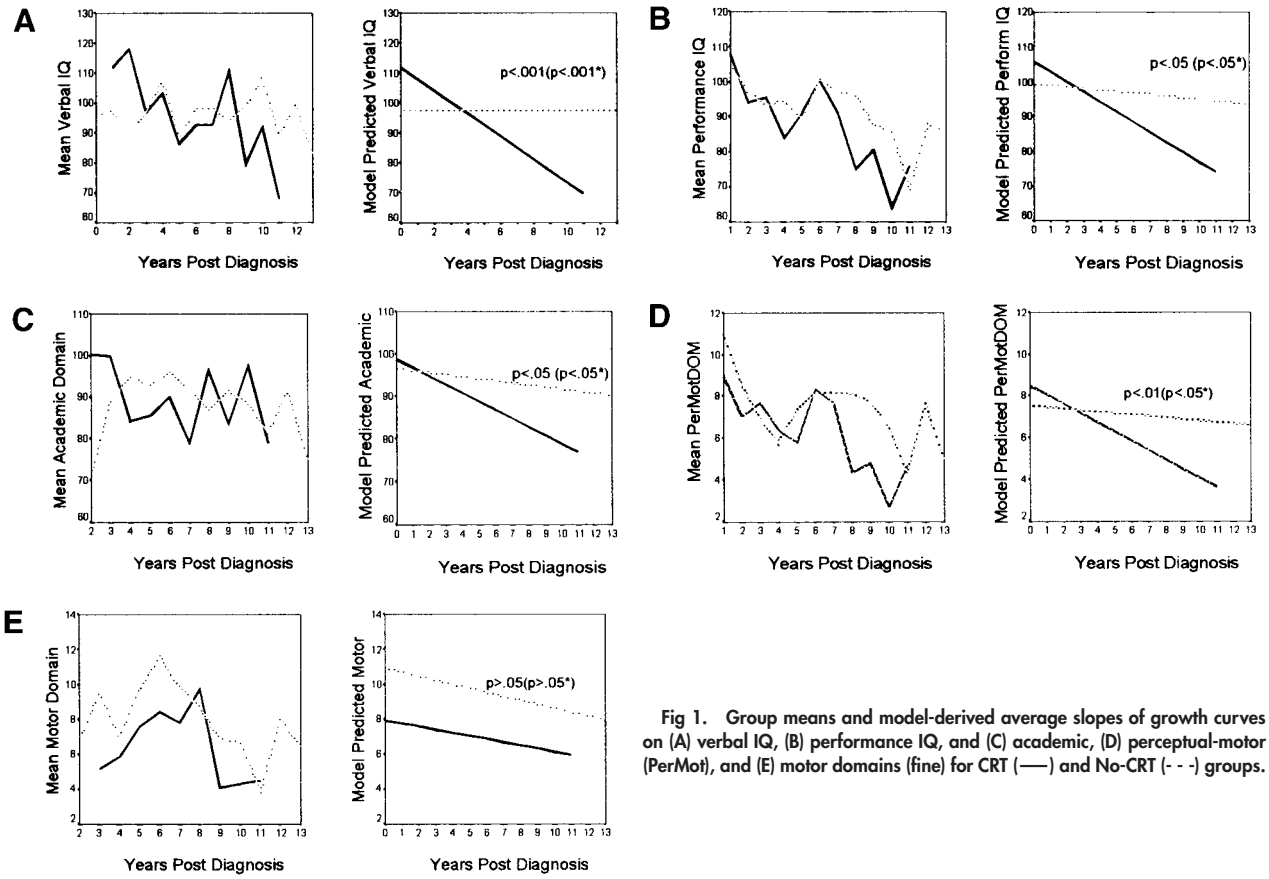

Fig 1. Group means and model-derived average slopes of growth curves on (A) verbal IQ, (B) performance IQ, and (C) academic, (D) perceptual-motor (PerMot), and (E) motor domains (fine) for CRT (——) and No-CRT (- - -) groups.

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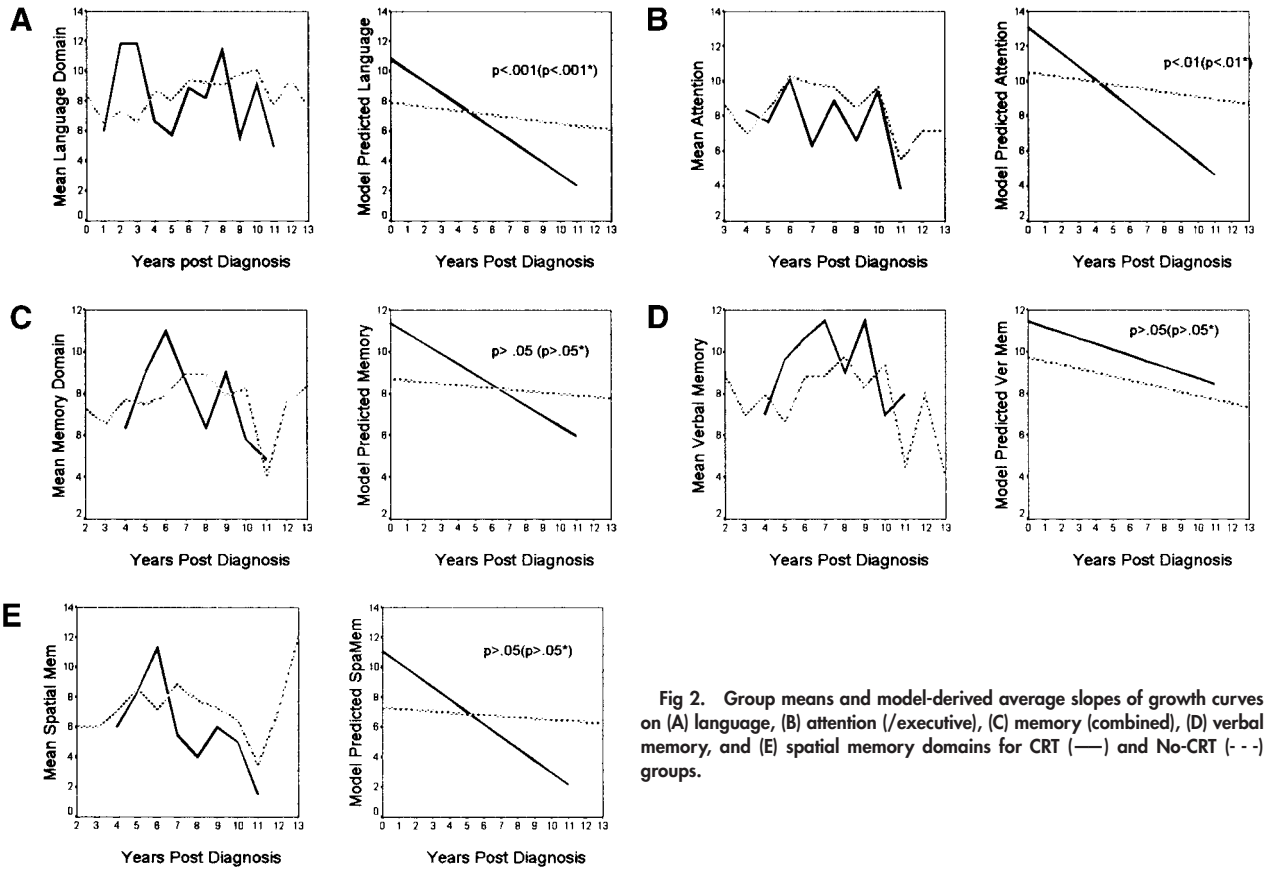

Fig 2. Group means and model-derived average slopes of growth curves on (A) language, (B) attention (/executive), (C) memory (combined), (D) verbal memory, and (E) spatial memory domains for CRT (——) and No-CRT (- - -) groups.

Language (Fig 2A) was highly significant ($P < .001$), with the radiated group showing a significant lag in development across time. Attention/executive domain (Fig 2B) was very significant as well ($P < .01$). Patients in the nonirradiated group managed to stay within the normal range, whereas patients in the irradiated group—who began with scores that were well above average—eventually declined to well below average.

The groups were not significantly different on the memory domain (verbal and spatial memory combined), although the irradiated group actually began with a higher score (Fig 2C). When the two types of memory were analyzed separately (Figs 2D and 2E), it can be seen that both groups declined at about the same rate on verbal memory (Fig 2D). However, on spatial memory (Fig 2E), the irradiated group's decline was more marked, and the difference in slope between the two groups approached significance ($P < .08$).

DISCUSSION

The effects of brain tumor treatment that consists primarily of surgery and chemotherapy are seldom addressed in neuropsychologic studies of children. Two that examined the effects of chemotherapy on children with posterior fossa tumors concluded that, except for methotrexate, chemotherapy did not seem to produce neuropsychologic effects.[9,22] Another study suggested that methotrexate was also responsible for adverse effects; however, because patients in that study also received CRT, it is not known whether the effects were from methotrexate and/or CRT.[8]

Our results, which show mean scores in the normal range for the group of patients whose treatment consisted only of surgery and chemotherapy, are consistent with those of Ellenberg et al[9] and Packer et al[21]; that is, we found that brain functions were spared when CRT was withheld. This finding of discrepant performance between irradiated and nonirradiated patients is particularly striking in the growth-curve analyses in the prospective study. The developmental progress of the two groups was significantly different on seven of the eight neurocognitive domains assessed, with much better preservation of skills among the nonirradiated patients.

Nevertheless, despite this optimistic picture, the nonirradiated group's scores did tend to decline somewhat across time, and their scores on specific memory and motor tests, although not impaired, were lower than in other domains.

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This might suggest that chemotherapy could be responsible, but the location of the tumor in the cerebellum may be important to consider as well.

Effects of disease location versus treatment has been an issue in previous research.[9,14-16] Some studies have compared patients with posterior fossa medulloblastoma who received CRT with those with cerebellar astrocytomas who were not irradiated and found that the astrocytoma patients outperformed those with medulloblastoma,[11,25,26] suggesting that damage was associated with CRT rather than tumor. Riva et al,[26] however, found that both of these groups performed less well than a control group. Likewise, LeBaron et al[17] noted that there were significant neuropsychologic impairments in patients with posterior fossa tumors who did not receive CRT. Jannoun and Bloom[14] found that their posterior fossa group had the lowest incidence of IQ deficits (only one of 12 patients). However, because they only administered an IQ test, it is not known whether their subjects had specific motor and memory impairments. In a recent study of children assessed at the time of diagnosis, our group found that those with posterior fossa tumors were already impaired in memory, motor, attention, and visual-spatial domains, suggesting tumor effect rather than treatment effect.[4]

The comparative effects of tumor versus treatment is not clear-cut in children with posterior fossa tumors. Making the issue still more complex is the impression that the specific neuropsychologic skills affected by posterior fossa brain tumors and their treatment tend to be similar to those found among leukemia patients who have received irradiation.[21,22,54,55] These encompass primarily nonverbal functions such as visual-spatial integration, attention, motor coordination, and mathematical skills.[6,10,16,17,19,27,28] Because some children with posterior fossa tumors show similar deficits even without CRT,[4,6,19] there is the possibility that the cerebellum, with its reciprocal neural connections with the thalamus, corpus callosum, and cerebral cortex, may be involved.[17,54,56-61] Fibers in the dentate nucleus of the cerebellum reciprocally connect with the association cortex of the frontal lobe via the thalamus, contributing to both motor and mental functions.[57] The cerebellum seems to contribute to timely, accurate performance of all systems with which it has functional interconnections (eg, sensory, motor, attention, and cognitive functions).[60] For example, with the brainstem, the cerebellum regulates motor reflexes; with sensorimotor areas, it allows skilled manipulation of muscles such as those for hands and speech; and with the prefrontal association cortex, it contributes to the manipulation of ideas that are involved in planning.[57]

In the few existing reports of mostly adult patients and some children with different kinds of cerebellar abnormalities, findings of impairments in executive skills (ie, planning, organization, and problem-solving), learning, attention, and visual-spatial processing are common.[33,58-67] In a recently published case study of a child, Schatz et al[68] demonstrated that persistent psychomotor slowing and deficits in these functions occurred in a 7-year-old girl with focal injury to the left cerebellum. Her scores at 13 and 16 months after injury demonstrated that the child was consistently slower than her peers on all tasks that measure these skills.

Because CRT affects similar areas of functioning, it is not possible to distinguish its effects from tumor effects in the irradiated subjects. However, we want to point out that patients who did not receive irradiation did not exhibit the same degree of loss in these skills, and that actually their lowest score was in verbal memory. So, tumor location within the cerebellum may be a factor, especially in view of Schatz et al[68] finding linguistic processing deficits in their patient. It is notable as well that our patients with tumors in the midline of the cerebellum were weakest on spatial memory and perceptual-motor skills, whereas those with tumors in the cerebellar hemispheres and the fourth ventricle were weakest in academic achievement and verbal memory. Because the sample size is very small, we will be evaluating this issue on a larger sample that includes older as well as younger children.

Another issue that should be evaluated with a larger sample is the effect of partial versus total resection of the tumor on neurocognitive outcome. A number of authors have pointed out the relevance of this factor to survival.[69,70] It is the case that the seven participants in this sample who had had partial resection were impaired on eight neuropsychologic domains, and as a group, they scored significantly lower than did the total resection group on verbal IQ and perceptual-motor scores. However, because four of the seven patients had received irradiation, the linkage with type of surgery is weakened. Therefore, the effect of partial versus total resection will be investigated in a subsequent study with a larger number of nonirradiated patients.

An important weakness of the current study is the small sample size and large number of statistical tests, both of which may limit the internal and external validity of the results. However, both the direction and magnitude of the effect of CRT in the prospective analysis is plausible in light of the recent literature, and our findings were consistent across seven domains of cognitive functioning. Moreover, different methods of fitting the statistical models were used to assess the stability of the findings and were found to yield similar results.

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The issue of balancing the chance for survival with long-term effects of the treatment frequently emerges in studies that implicate CRT in compromised outcomes. Fortunately, studies reporting comparable survival of infants treated with chemotherapy compared with those treated with CRT are appearing in the literature.[70-72] Ater et al[70] reported that the long-term (> 5 years) survival rate of 17 infants and young children with brain tumors was almost 60%, and thus they conclude that omitting cranial irradiation unless relapse occurs is a valid approach, providing good rates of survival.

Despite recent progress in modifying the treatment of brain tumors, many of the survivors in this study were found to have neurocognitive and psychosocial deficits that required remediational interventions. Fortunately, preliminary studies of programs designed for such children and adolescents are beginning to yield promising results.[73,74] These programs emphasize practice and repetition, strategy acquisition, behavioral therapy, and parent consultation, and efforts are made to help the participant apply the skills learned in the school environment. However, long-term, multi-institutional studies are needed to demonstrate their ultimate effectiveness on academic outcome.

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