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Cognitive deficits in long-term survivors of childhood brain tumors

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Abstract. Improvements in survival for patients who had childhood brain tumors has led to an increasing emphasis on the quality of life for these long-term survivors. Initial survival studies relied on global descriptions of functional abilities to assess cognitive deficits and reported that from 20% to 40% of long-term survivors had obvious partial disability and <10% were severely disabled. Formal neuropsychological testing has revealed that from 40% to 100% of long-term survivors have some form of cognitive deficit in various intelligence quotients, visual/perceptual skills, learning abilities, and adaptive behavior. Prospective, controlled studies have found a younger age at diagnosis, radiotherapy, methotrexate chemotherapy, tumor location and time interval to testing to be important (alone or in combination) and related to a high risk of subsequent cognitive deficits. Some variables play an as yet unresolved role. However, despite the progress of the last decade, future prospective studies are needed to define the role of certain variables in the development of cognitive deficits that maximize survival while minimizing cognitive deficits.

Key words: Childhood brain tumors – Long-term survivors – Cognitive deficits

Slow, but definite progress has occurred in the treatment of pediatric brain tumors during the past 20 years. As 5- and 10-year survival rates have improved, so has concern over the quality of life and cognitive deficits exhibited by the long-term survivors. This review examines the various studies that have molded our current understanding of this dilemma.

There are three sections in this review. The first reviews the neuropsychological tools used by studies designed to detect cognitive sequelae in long-term survivors. The second recounts studies published between 1968 and 1989 that depict the incidence and severity of these cognitive deficits. In the third section, the various factors purported to play a role in the pathogenesis of these cognitive deficits are described and discussed.

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Assessment of cognitive deficits

Initial methods of evaluation

The first attempts at depicting cognitive deficits in the late 1960s and mid-1970s involving either an analysis of school performance or placement, the presence or absence of "mental retardation" (determined without the use of norm-referenced tests) or a global assessment of daily functioning. Two major classifications based on daily functioning ability were proposed by Bouchard [8] and Bloom et al. [6] (Table 1).

Introduction of norm-referenced tests

Since the late 1970s studies of long-term survivors of childhood brain tumors have employed various norm-referenced tests to document cognitive deficits (Table 2).

General intelligence tests

The most frequently employed category of neuropsychometric tests are the general intelligence tests [34]. The Wechsler Intelligence Scale for Children – Revised (WISC-R), useful for children between 6 and 17 years old, calculates three separate intelligence quotients (IQ): a Full Scale IQ (FSIQ), a Verbal Scale IQ (VIQ), and a Performance Scale IQ (PIQ). Patients older than 16 years are assessed using the Wechsler Adult Intelligence Scale – Revised (WAIS-R), which also provides a FSIQ, a VIQ, and a PIQ. A third general intelligence test is the Stanford-Binet Intelligence Scale, used in children between the ages of 2 and 24 years.

Table 1. Bouchard and Bloom classifications

Bouchard classification	
Category I:	"Patients who return to an active, useful life"
Category II:	"Patients who are partially disabled either physically or mentally"
Category III:	"Patients who are so severely incapacitated following treatment that they are incapable of an independent existence"
Bloom classification	
Category I:	"No disability, active life. Patients in this group have no abnormal neurologic signs other than nystagmus. Children who are said to be slow at learning, but who, on general examination, are bright and appear intelligent"
Category II:	"Mild disability, active life. Here there may be ocular paresis, limited intention tremor and mild ataxia"
Category III:	"Partial disability. Patients may be severely ataxic or have seriously reduced vision, but all are capable of self-care. They may have definite impairment of intellect, but are capable of being taught a trade"
Category IV:	"Total disability. These cases are incapable of self-care"

Table 2. Neuropsychometric tests used in evaluating cognitive deficits (and studies employing the test)

General intelligence tests
Wechsler Intelligence Scale for Children – revised [7, 10–14, 19, 21–23, 26, 27, 30, 31, 35]
Wechsler Adult Intelligence Scale – revised [7, 13, 23, 31, 35]
Standford-Binet Intelligence Scale [3, 12, 13, 31]
Specialized intelligence tests
Bayley Scales of Infant Development [14, 31]
McCarthy Scales of Children's Ability [7, 13, 14, 21, 22, 26, 35]
Achievement tests
Wide-Range Achievement Test (WRAT) [10–12, 26, 27, 30, 35]
Peabody Individual Achievement Test (PIAT) [21, 23]
Visual/perceptual motor tests
Bender Gestalt [10, 12, 35]
Development Test of Visual Motor Integration [30, 31]
General batteries
Halstead Battery [23]
Reitan Battery [12, 23]
Adaptive behavior scales and checklists
Vineland Social Maturity Scale [30]
Child Behavior Checklist (CBC) [23]
Personality Inventory for Children (PIC) [21, 22, 26, 27]
Louisville Behavior Checklist (LBC) [26]

Specialized intelligence tests

The three general intelligence tests described above do not permit adequate assessment of cognitive skills in infants or young children [34]. The Bayley Scales of Infant Development provides an assessment of infant development between the ages of 2 months and 2.5 years. The results are expressed as a Mental Development Index and a Psychomotor Development Index. The cognitive abilities of children between the ages of 2.5 years and 8.5 years can be assessed using the McCarthy Scales of Children's Abilities. Overall, a General Cognitive Index (GCI) which is comparable to an intelligence quotient, can be generated.

Achievement tests

Separate from the estimation of innate intelligence is the assessment of academic achievement [34]. A widely used achievement test is the Wide Range Achievement Test – Revised (WRAT-R). Results can be converted into standard scores, percentile ranks or grade-equivalent scores. A second major achievement test is the Peabody Individual Achievement Test (PIAT), which is applicable to all school age children.

Visual/perceptual motor tests

The most commonly used test of visual/perceptual motor development in children between 5 and 8 years of age is the Bender Visual Motor Gestalt Test [34]. By itself, the Bender Gestalt *cannot* be used to make a diagnosis of "brain damage", mental retardation, or autism. Another useful test of visual/perceptual motor ability is the Developmental Test of Visual-Motor Integration (DTVMI) [4].

General batteries

Some neuropsychologists employ a battery of tests in order to document the existence of "brain damage" [34]. The two best-known batteries are the Halstead-Reitan Neuropsychological Test Battery for Older Children (Halstead Battery) and the Reitan-Indiana Neuropsychological Test Battery for Children (Reitan Battery). Both these batteries are used by neuropsychologists to document and localize an organic cause for cognitive deficits detected [34].

Adaptive behavior scales and behavior checklists

Cognitive deficits may manifest themselves as deficits in adaptive behavior which can be assessed by the Vineland Social Maturity Scale (VSMS) or its revision, the Vineland Adaptive Behavior Scales (VABS) [34]. Another method of determining abnormalities in adaptive behavior is through the use of behavioral checklists answered by parents or guardians. Checklists used in the assessment of brain tumor patients include the Child Behavior Checklist (CBC), the Personality Inventory for Children (PIC), and the Louisville Behavior Checklist (LBC).

Depiction of cognitive deficits in survivors

Since 1968 at least 30 studies have commented on the incidence and severity of cognitive deficits in long-term

Table 3. Cognitive deficits in tumor studies (1968–1989)

Study (year, study size)	Study format	Age at diagnosis (years)	Follow-up interval (years)	Results
Fessard (1968, $n=11$)	R, U	<2	2–14	27% debilitated or backward
Bloom et al. (1969, $n=22$)	R, U	<15	5–17	18% Bloom III or IV 30% slow learners
Jenkin (1969, $n=30$)	R, U	<16	4–19	3% mental retardation 10% learning problems
Aron (1969, $n=5$)	R, U	<15	1.8–22	40% borderline mental retardation 20% slow learner
Marsa et al. (1973, $n=18$)	R, U	9 (median)	1–11	39% Bouchard category II 6% retarded, 6% learning difficulty
Abramson et al. (1974, $n=65$)	R, U	<18	2	22% Bouchard category II 1 % Bouchard category III
Onoyama et al. (1975, $n=42$)	R, U	<15	3–15	21% Bouchard category II 10% Bouchard category III
Bamford et al. (1976, $n=30$)	R, U	<15	8–18	43% "educationally subnormal or severely subnormal"
Gjerris (1976, $n=74$)	R, U	<14	15–40	5% "mentally retarded" 4% "dementia"
Harisiadis and Chang (1977, $n=11$)	P, U	6.25 (median)	5–13	36% special education
Mealey and Hall (1977, $n=9$)	R, U	8 (median)	3–13	22% mild mental retardation
Farwell et al. (1978, $n=18$)	R, U	<1.5	1–23	22% institutionalized 11% school for retarded children
Raimondi and Tomita (1979, $n=13$)	R, U	4.5 (median)	2–10	23% retarded
Hirsch et al. (1979, $n=33$)	R, C	5 (median)	>1	31% IQ<70, 27% Bloom III or IV 82% specific learning disabilities
Broadbent et al. (1981, $n=8$)	R, U	<14	5–10	38% "frank mental retardation"
Berry (1981, $n=68$)	R, U	7 (median)	5–10	12% mental retardation, paraplegia, blindness
Spunberg et al. (1981, $n=14$)	R, U	<2	5–19	44% FSIQ<70, 42% VIQ<70, 60% PIQ<70, 93% learning problems
Danoff et al. (1982, $n=38$)	R, U	7.9	9.3 (mean)	17% IQ<70, 11% Bloom III or IV 37% emotional/behavioral problems
Duffner et al. (1983, $n=10$)	R, U	3 (median)	1	50% IQ<80, 100% dementia, mental retardation, or learning problems
Raimondi and Tomita (1983, $n=15$)	R, U	<1	1–10	33% mental retardation
Chin and Maruyama (1984, $n=23$)	R, U	1.5–12	8.5 (median)	20% mental deficient
Kun et al. (1983, $n=30$)	R, U	6 (median)	1.75 (meadian)	9% FSIQ<70, 11% VIQ<70, 8% PIQ<70, 63% learning disabled
Kun et al. (1983, $n=18$)	R, U	6 (median)	1.8, 3.5 and 4.1	28% FSIQ, VIQ, PIQ<80 (1st evaluation); no significant change over 3 evaluation
Mulhern and Kun (1985, $n=26$)	P, U	7.75	0.5	FSIQ 99, VIQ 103, PIQ 96, GCI 99; 19% had one or more subtests <80
Ellenberg et al. (1987, $n=43$)	P, C	7.5 (mean)	<4	9% Bloom IV, 40% Bloom III
Packer et al. (1987, $n=24$)	R, U	7.75	5	FSIQ 97, >50% had learning, fine motor, memory problems
Lebaron et al. (1988, $n=15$)	R, U	8.3	1.6 (median)	Mean FSIQ 77, 20% had FSIQ<70 20% Bloom III or IV
Mulhern et al. (1988, $n=7$)	P, U	8.4 (median)	0.7, 3.0 (median)	28% FSIQ<70, 71% learning disability
Duffner et al. (1988, $n=16$)	P, U	8 (median)	3–7	9 point drop in mean IQ over 3 or more years, 94% learning problems
Bordeaux et al. (1988, $n=14$)	P, C	10	0.1–0.9	FSIQ 104–107, language and fine motor problems pre- and post-therapy
Packer et al. (1989, $n=23$)	P, C	7.7 (median)	2	RT group: FSIQ dropped 14 points; non-RT group: FSIQ no change

survivors of childhood brain tumors. Many of the earlier reports focused on factors involved in survival rather than long-term cognitive deficits and tended to be retrospective and uncontrolled and relied on global descriptions of cognitive deficits. This section will review studies (beginning in 1968) that depict the cognitive deficits seen in long-term survivors of childhood brain tumors (Table 3).

In 1968, Fessard reported that 45% (5/11) of his long-term survivors were normal (all with posterior fossa tumors), but 27% (3/11) were deemed to have "debility or backwardness" [16].

In a landmark study published in 1969, Bloom described the outcome of 22 long-term survivors with primitive neuroectodermal tumor/medulloblastoma (PNET) [6]. All underwent surgery, most finished a complete radiotherapy course, and none received chemotherapy. Eighty-two percent (18/22) of the long-term survivors were either Bloom category I or II, 9% (2/22) category III, and 9% (2/22) category IV.

Two other studies published the same year shed light on the cognitive deficits seen in survivors of childhood PNET. Jenkin reported only 1 of 47 patients (3%) showed "progressively more evidence of mental retardation" and 3 (10%) "dropped at least one grade during their subsequent schooling" [20]. Aron described the outcome of 5 long-term survivors of PNET (treated with craniospinal radiation) and found 2 of 5 patients (40%) were either "borderline mental defective" or had "mental status slightly below normal" and one (20%) was a "slow learner" [2].

Bouchard's functional categories

Between 1973 and 1975 three articles appeared which utilized the Bouchard categories to describe long-term outcome. In 1973 Marsa reviewed the results of 18 children with astrocytic gliomas in different locations, treated with different degrees of surgical resection and differing amounts of radiotherapy [24]. Thirty-nine percent (7/18) had a fair quality of life (Bouchard category II), while the remainder were leading normal lives. Six percent (1/18) were mentally retarded and 6% (1/18) had learning difficulties.

The outcome of 65 long-term survivors of a variety of brain tumors treated in a heterogeneous fashion was described by Abramson et al. [1]. Twenty-two percent (14/65) were felt to be in Bouchard category II and 1% (1/65) was placed in category III. In 1975, Onomaya documented the Kyoto University Medical Center experience with 42 long-term survivors of childhood brain tumors; 21% (9/42) were Bouchard category II, 10% (4/42) were category III, and the remaining 69% (29/42) were category I [28].

Bamford's change in approach: focusing on deficits

In 1976, among an "unselected sample of 30 children," out of 64 long-term survivors Bamford et al. found 10% (3/30) to be superior, 33% (10/30) average, 13% (4/30) below average, 7% (2/30) "severely subnormal" and 37% (11/30) "educationally subnormal" [3]. Emotional problems, including depression, lability, suicide attempts, and aggressive behavior, plagued 43% (13/30) of the survivors. Overall, 80% (24/30) had a residual problem with 20% (6/30) profoundly disabled.

End of the summary studies

Multiple articles appeared in the late 1970s that shed additional light on the incidence and magnitude of cognitive deficits in long-term survivors despite not employing formal neuropsychological testing. Gjerris found cognitive deficits, including "dementia" in 4% (3/74) and "mental retardation" in 5% (4/74) of patients evaluated [17]. Overall, 4% (3/74) were in need of nursing home care and 16% (12/74) "were receiving disablement pension." Harisiadis found 36% (4/11) of long-term survivors needed special education and exhibited language problems [18].

In 1977, Mealey concluded that 22% (2/9) of long-term survivors "required special education for mild mental deficiency," 67% were normal, and 11% (1/9) had a "nonincapacitating cerebellar ataxia" [25]. Among 18 children who survived longer than 1 year, Farwell found 22% to be "institutionalized" and 11% attending "schools for retarded children" [15].

Raimondi reported, in 1979, that 38% (5/13) of children surviving more than 2 years following diagnosis of PNET were "living completely normal lives," and 23% (3/13) were noted to have "psychomotor retardation" [32]. A second article by Raimondi [33], focused on 15 long-term survivors of primary intracranial neoplasms. Overall, 33% of the long-term survivors were "retarded"; all had received radiotherapy. The 6 patients who did not undergo radiotherapy had either teratomas or papillomas and were normal.

Introduction of detailed neuropsychologic testing

Formal neuropsychological testing was used by Hirsch in 1979 to detect cognitive deficits in 33 long-term survivors of PNET [19]. All underwent surgery and a course of radiotherapy. Craniospinal radiation consisted of 5000 rads to the posterior fossa and 3500 rads to the cerebral hemispheres and spinal cord (children under 3 years received 500 rads less to each region). Chemotherapy was used extensively, including intrathecal methotrexate, vincristine and 1-(-2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU).

Hirsch employed the WISC and two neuropsychological tests not used in the United States. He found 31% (8/26) had an IQ < 70, 58% (15/26) had an IQ < 90, and the remaining 11% (3/26) had an IQ > 90. Emotional and behavioral disorders were very common in the survivors, occurring in 93% (26/28). Fifteen percent of long-term survivors (5/33) were in Bloom category III and 12% (4/33) were in category IV. A major feature of Hirsch's

article was the use of a "control group" of 31 children with cerebellar astrocytoma. Among the astrocytoma group 19% (6/31) had an IQ < 70, 19% (6/31) had an IQ between 70 and 90, and the remaining 62% (19/31) had an IQ > 90. Emotional and behavioral disorders occurred in 59% (19/31).

PNET review articles

Broadbent et al. reported that out of 8 long-term survivors with confirmed PNET, treated by surgery and then craniospinal irradiation, 62% (5/8) were at "normal schools" while the other 38% (3/8) showed evidence of "frank mental retardation" [9].

Berry and Jenkin described 68 long-term survivors and noted that 12% (8/68) exhibited "major deficits: mental retardation, paraplegia, and blindness" while 28% (19/68) were reported to have had unspecified "moderate neurological deficits" [5, 20].

Neuropsychologic testing and the 1980s

The two most important changes which occurred in the study of cognitive deficits during the first half of the 1980s were the increasing use of neuropsychological testing and the development of prospective studies.

The first study of this group was published by Spunberg et al. [35]. Among 14 survivors of primary brain tumors (43% supratentorial, 57% infratentorial), diagnosed under the age of two years, 79% (11/14) had undergone surgery and all had received localized radiotherapy. Intelligence testing revealed 44% (4/9) had FSIQ < 70, 93% (12/13) had learning problems, and 46% (6/13) needed special education.

Danoff et al. (1982) reported the cognitive results of 38 children with a variety of brain tumors (71% supratentorial, 29% infratentorial) [11]. All but 1 patient underwent surgery, all patients received radiotherapy, and none received chemotherapy. The radiotherapy ranged from 4000 to 6500 rad with 82% (31/38) receiving 5000 to 5600 rad. Seventeen percent (6/36) had an IQ < 70; 37% (14/36) had "emotional problems and behavioral disturbances"; 11% (4/38) were classified as Bloom category III or IV.

Duffner et al. described the cognitive deficits in a group of 10 long-term survivors of posterior fossa tumors; all had undergone surgery, radiotherapy, and chemotherapy [12]. Radiotherapy included 2000 to 5040 rad to the posterior fossa with 2635 to 4000 rad to the whole brain. All patients received both intrathecal and intravenous methotrexate, intravenous vincristine, BCNU, and dexamethasone. Fifty percent (5/10) had an IQ below 80, including 2 with IQ < 20. Duffner et al. found that all patients surveyed suffered from either dementia, learning disabilities, or mental retardation. A second study by Duffner et al. showed a drop in mean IQ among 16 children with brain tumors (63% supratentorial, 37% infratentorial) from a pretreatment level of 93.5 to 84.5 three or more years later [13]. All had undergone surgery and radiotherapy, but only 31% (5/16) received chemotherapy (methotrexate in only 2 patients). Ninety-four percent (15/16) had learning disabilities and 69% needed special education.

In 1984, Chin and Maruyama reported the neuropsychological performance results of 10 children with PNET [10]. All had undergone postoperative radiation therapy. Passing note was made of the use of chemotherapy in these children without a full description of type, route of administration, or dose. Both patients (20%) less than 4 years old were deemed "mental deficient". Although this article used multiple neuropsychological tests, neither summary data nor analysis based on FSIQ, VIQ, or PIQ was presented.

Long-term cognitive deficits in a series of 24 children with only PNET treated between 1975 and 1984 was reported by Packer et al. in 1988 [30]. Following surgery, patients > 2 years old received 4000 cGy (median) craniospinal radiation with a local tumor boost to 5200 cGy (median) while children < 2 years old received between 1800 and 2000 cGy craniospinal radiation with a local tumor boost to between 4500 to 4600 cGy. Chemotherapy included CCNU, vincristine, and prednisone, but none received intrathecal medication. Neuropsychological tests revealed a median FSIQ ($n = 17$) of 97 (range 20–126), median VIQ of 101 and median PIQ of 94. Fifty-four percent (13/24) were in special education placement. Vineland social maturity scale assessments were abnormal in 25% (2/8) with a mean score of 88.

Lebaron et al. retrospectively examined the quality of life in 15 long-term survivors of mixed posterior fossa tumors [23]. All underwent surgical resection but only 11 had irradiation. One patient received an unknown type and amount of chemotherapy in addition to the radiotherapy. The mean FSIQ, VIQ, and PIQ were 77, 77, and 81, respectively; 20% (3/15) had FSIQ below 70. Both major general neuropsychological batteries were employed. Two subtests involving cognitive flexibility (The Category Test and Trail Making Test B) revealed serious impairment in 20% (3/15) and 72% (5/7) of the children, respectively. Most (11/15) were either in special education, had repeated a grade, or had not returned to school.

Mulhern et al. reported the neuropsychologic functioning of 7 children with temporal lobe astrocyomas treated between 1975 and 1984 [27]. Following surgery, all underwent local radiotherapy (5000 to 5800 cGy) and 1 had 3600 cGy to the whole cranium. Twenty-eight percent (2/7) had FSIQ < 70 while 43% (3/7) had 70 < FSIQ < 90; 43% (3/7) exhibited intellectual deterioration in FSIQ over the time of the study. Special educational classes were needed in 71% (5/7) and 14% (1/7) were deemed "educable mentally retarded."

Prospective studies

Kun and Mulhern detailed the neuropsychological alterations over time in long-term survivors in a series of articles published between 1983 and 1985. The first article, in 1983, scrutinized 30 children with primary brain tumors (50% supratentorial, 50% infratentorial) treated

between 1979 and 1981 [22]: 87% (26/30) underwent surgery and 70% (21/30) received radiation therapy ranging from 4000 to 5800 rad. Adjuvant chemotherapy (BCNU, vincristine, and cyclophosphamide) was used in 3 patients. Overall, 9% (2/23) had FSIQ <70 and 7% (2/30) had memory scores below 70. Kun determined abnormal social-emotional functioning using the PIC and found that 62% (13/21) of the children tested scored in the "at risk" or "deviant" range. Sixty-three percent (10/16) of the patients needed special education. Their second article examined 18 children with serial neuropsychologic evaluations [21]. Initially, 28% (5/18) had FSIQ <80 and 28% (5/18) had memory scores below 80; these percentages did not significantly differ at the second evaluation.

The last article in this series prospectively examined 26 children with primary intracranial neoplasms (58% supratentorial, 42% infratentorial) [26]. Surgery was performed in 88% (23/26) of the cases and radiotherapy in 96% (25/26). Initial evaluations, performed post-surgery and preradiotherapy, revealed normal FSIQ, VIQ, PIQ, and CGI. Six months after radiotherapy was completed, the FSIQ, VIQ, PIQ and GCI were essentially unchanged. PIC or LBC revealed between 42% and 50% of the children were manifesting symptoms of emotional disturbance.

In the 1987 prospective study of Ellenberg et al., the intellectual outcome of 43 patients with primary intracranial neoplasms (49% supratentorial, 51% infratentorial) was serially assessed [14]. Ninety-three percent (40/43) underwent craniotomy and 86% (37/43) received radiotherapy, 43% (14/43) of the patients received chemotherapy, including cytoxan [9], vincristine [9], prednisone [10], procarbazine [10], CCNU [3], 5-fluorouricil [2], but not methotrexate; 9% (4/43) of the patients were Bloom category IV, 40% (17/43) category III, 33% (14/43) category II, and 19% (8/43) category I.

Bordeaux et al. serially evaluated 14 children with primary brain tumors treated between 1983 and 1985 [7]. Fifty percent (7/14) only had surgery while the other 50% (7/14) were treated by surgery followed by radiotherapy. Bordeaux analyzed the two groups separately. The 7 children treated by surgery alone (median age 124 months) had normal pre- and postsurgical FSIQ, VIQ, PIQ, and WRAT scores. Fine-motor speed, visual motor construction, and psychomotor speed were statistically significantly lower than age norms, but no statistically significant changes over time were detected for any variable. In fact, mean scores improved after surgery in 22 out of 26 test variables.

All 7 children treated with surgery and then radiation received local irradiation; 4 also underwent-whole-brain irradiation, and 3 were given spinal radiotherapy. The mean pre- and postradiation FSIQ, VIQ, and PIQ were normal. Expressive language skills and fine-motor speed were statistically significantly lower than age norms, but there was no statistically significant change over time. In fact, group scores improved in 12 out of 26 test variables after radiation.

Packer conducted a prospective controlled study of the effects of radiotherapy in 18 children (median age 7.7 years) treated between 1983 and 1986. All patients underwent surgery, followed by radiation therapy. Children between 18 and 36 months of age at diagnosis received 2400 cGy of whole-brain radiotherapy plus a boost of 2400 to 2600 cGy to the primary tumor site. Children above 36 months of age at diagnosis received 3600 cGy of whole-brain radiotherapy plus a boost of 1800 to 2000 cGy to the tumor site. Seventy-two percent (13/18) of the patients received chemotherapy, including cis-platinum, CCNU, and vincristine. Neuropsychological testing revealed baseline FSIQ, VIQ, and PIQ for this group were 105, 109, and 102, respectively. By year 1 the FSIQ, VIQ, and PIQ had all dipped to 97, 106, and 97, respectively. However, by the 2-year mark the FSIQ, VIQ, and PIQ had further dropped to 91, 102, and 97, respectively. Two years following therapy, 14% (2/14) had FSIQ <70. Visual motor impairments were seen initially in 18% (2/11) and after 2 years 43% (6/14) exhibited impairment. Sixty-seven percent (12/18) of this group required special education. Packer's control group consisted of 14 patients with cerebellar astrocytomas. None of the children received any radiation or chemotherapy. Baseline IQ scores were FSIQ 105, VIQ 109, and PIQ 98. After 1 year the scores were FSIQ 109, VIQ 115, and PIQ 101. After 2 years FSIQ was 106, VIQ 108, and PIQ 109. There was no increase during the 2 years of the study in the 14% to 21% of children exhibiting either fine motor, visual motor, memory, or language impairments at baseline. Seven percent of the control group required special education.

Parameters associated with cognitive deficits

The variables purported to be related to cognitive deficits can be divided into three groups: pretreatment, treatment, and post-treatment (Table 4).

Pretreatment variables

There are four pretreatment variables that have been examined for their relationship to the development of cognitive deficits: age at diagnosis, site of tumor, obtundation, or hydrocephalus.

Age at diagnosis

Danoff reported an IQ <70 in 60% (3/5) of the children between 1 and 3 years old, 11% (3/26) of the children between 3 and 11 years old, and 0% (0/5) of the group older than 11 years old [11]. Chin and Maruyama found that patients less than 4 years old at the time of therapy had "major learning disabilities," while patients older than 8 years old had "no major intellectual deficits" [10]. Packer et al. reported a trend toward association between lower FSIQ and age less than 7 years old at diagnosis. The mean IQ for children less than 7 years old was 92, between 7 and 10 years old it was 93, and for patients over 10 it was 104 [30]. Duffner et al. reported that a younger

Table 4. Parameters associated with congitive deficits and studies addressing parameter

Parameter	Studies supporting	Studies against
Pretreatment		
Younger age at diagnosis	[10, 11, 13, 14, 21, 26, 27, 30]	[22]
Site of tumor	[11, 14, 19]	None
Obtundation	[30]	None
Hydrocephalus	[3, 6]	[11, 14, 22]
Treatment		
Surgery	None	[7]
Extent of resection	[30]	[14]
Chemotherapy	[13]	[14, 30]
Radiation and chemotherapy	[12, 13]	None
Radiation	[13, 14, 19, 22, 31]	[6, 7, 10, 11, 35]
Post-treatment		
Ventricular dilation or need for permanent shunt	[30]	[14, 19]
Complicated postoperative course	[27, 30]	None
Poor seizure control	[27]	None
Tumor recurrence	[27]	None
Long interval after treatment	[13, 31]	[21, 22]

age appeared to "influence the development of dementia" [13].

In the first Kun and Mulhern article, no statistically significant association between age and any intellectual parameter could be found [22]. However, a trend toward a deficit in selective attending was noted in the younger age group in their second article [21]. In the third article of their series Mulhern and Kun found 63% of the children <6 years old had "deterioration on one or more intellectual parameters" [26] compared with only 11% of the children >6 years old. Their conclusion was that "younger children exhibited a greater tendency toward intellectual deterioration" [26]. This conclusion was reinforced when Mulhern found 75% (3/4) of the children with temporal lobe astrocytomas less than 8 years 5 months at diagnosis suffered intellectual deterioration, while none of the patients older than 8 years 5 months at diagnosis had an IQ <80 [27].

Ellenberg et al. [14] divided his patients into two age groups and at initial assessment the younger group (YG) had a group IQ of 99.7, while the older group (OG) had a group IQ of 84.9 ($P<0.005$). By the 4-month mark the OG's IQ had risen to 95.5. However, by the 1-year mark the YG's IQ had fallen 10.4 points (from 97.8 to 87.4, $P<0.05$) while the OG's IQ had stayed stable. By the 2–4 year mark, both groups had dropped, but only the OG's drop was significant (97.0 to 92.5, $p<0.05$). The combined effect of radiation and age was analyzed and will be presented below under the heading of radiation.

Site of tumor

Few investigators have analyzed the effect of tumor site in cognitive outcome. Hirsch et al. found 56% (5/9) of children with PNET involving the brainstem had IQs <70 compared with 18% (3/17) of children with PNET not involving the brainstem and concluded that "it is clear in our study that the neuropsychological sequelae are more frequent when the medulloblastoma adheres to the brainstem" [19].

In the 1982 study, Danoff et al. 62% (5/8) of the children with tumor extension to the hypothalamus had an IQ <70 while only 4% (1/28) of the patients without tumor extension to the hypothalamus had an IQ <70 ($P<0.05$). Danoff concluded that "the mental retardation in these patients is related primarily to the age at time of treatment and the tumor location" [11].

The patients in the study of Ellenberg et al. were divided into three tumor location groups (IV ventricle tumors, III ventricle tumors, and hemispheric tumors) and their IQ changes analyzed with respect to tumor site [14]. The mean IQ of the patients with hemispheric tumors was lower than the other groups "at all testing points" and attained statistical significance at the 4-month post-diagnosis mark. The mean IQ for patients with III ventricle tumors remained stable while the mean IQ of the IV ventricular tumor group exhibited a statistically significant drop between not only the 4th month and 1-year mark post-diagnosis (102.3 to 95.8, $P<0.05$) but also between the 4th month and the 2- to 4-year mark post-diagnosis.

Pretreatment obtundation

Packer et al. found the mean IQ of patients obtunded at the time of diagnosis was 67 compared with a mean IQ of 99 for the children with a normal mental status at diagnosis ($P=0.02$) [30].

Hydrocephalus at diagnosis

Both Bloom et al. and Bamford et al. felt that hydrocephalus played a definite yet unclear role in cognitive deterioration but did not present supportive data [3, 6]. On the contrary, Danoff et al. found that while 18% (4/22) of the children with hydrocephalus had an IQ <70, 14% (2/14) of the children without hydrocephalus also had an IQ <70 [11]. A similar result was shown by Kun [22].

In the study by Ellenberg et al. a group of 11 children without hydrocephalus had statistically significantly lower mean IQ scores than a group of 21 children with hydrocephalus at both the initial and 4-month testing marks. Ellenberg et al. concluded that "the acute hydrocephalus associated with pediatric brain tumors was not found to be a potent contributor to long-term IQ changes in these patients" [14].

Treatment

There are five treatment variables that have been examined for their relationship to the development of cognitive

deficits: surgery, extent of resection, nonmethotrexate chemotherapy, radiation and methotrexate chemotherapy, and radiation.

Surgery

Bordeaux's 1988 study concluded that surgery itself was not associated "with acute effects on neuropsychological functions" since there was no statistically significant difference between presurgical test scores and postoperative scores [7].

Extent of resection

Packer et al. reported patients with a total resection had a mean IQ of 98 compared to a mean IQ of 60 in patients with less than a total resection ($P < 0.025$) [30]. In contrast, Ellenberg et al. found "no significant difference in mean IQ between" patients with gross total resection and children having either a partial resection or biopsy "at 1 or 4 months postoperation or at long term follow-up" [14]. In the Ellenberg et al. study mean IQ scores for both the gross total resection group and the partial resection/biopsy group ranged from approximately 88 to 98 at all testing points.

Nonmethotrexate chemotherapy

Methotrexate is a well-known neurotoxic chemotherapeutic agent and will be discussed in more detail in the next section. Ellenberg et al. found no significant difference in mean IQ among the 9 patients who received nonmethotrexate chemotherapy (cytoxan, vincristine, prednisone, procarbazine, CCNU, and 5-fluoruracil) and the 25 children who received no chemotherapy at either "4 months postdiagnosis". . ."or at the 1 to 4 year follow-up examination" [14]. Packer et al. evaluated nonmethotrexate chemotherapy as a factor in cognitive outcome and did not find any statistically significant associations [30]. However, in Duffner's second study three patients treated with nonmethotrexate-containing regimens suffered IQ drops of 14, 28, and 9 over 3 years. Duffner et al. concluded that even nonmethotrexate chemotherapy was a "significant factor in treatment associated dementia" [13].

Radiation and methotrexate chemotherapy

An important subsection of the radiation therapy controversy (elaborated on at length in the next section) is the effect on cognitive function when radiotherapy is combined with methotrexate (either intrathecal or intravenous). Duffner found in her first study that all 10 of the patients treated with both methotrexate (both intrathecal and intravenous) and radiotherapy had either "dementia, learning disabilities, or evidence of intellectual retardation" [12]. In her second study the combination of radiotherapy and methotrexate in 2 patients led to IQ drops of 14 and 29 points. Duffner et al. concluded that "chemotherapy, particularly a regimen involving methotrexate, appears to be a significant factor in treatment associated dementia" [13].

The combination of radiotherapy and methotrexate can give rise to the syndrome of necrotizing leukoencephalopathy (NP) [29]. NP consists clinically of a variety of symptoms (including developmental regression, dementia, spasticity, ataxia, seizures, hemiplegia, and pseudobulbar paresis), beginning usually 4 to 12 months after completing radiotherapy. Histologically, NP is characterized by multifocal areas of coagulation necrosis in the deep white matter with diffuse reactive astrocytosis. Although NP can occur in patients undergoing radiotherapy alone or receiving methotrexate alone, the combination of the two treatment modalities significantly elevates the incidence of NP.

Radiation

Since radiation therapy (RT) was first shown to increase survival, its long-term effects on cognitive function have been very controversial. Bloom et al. felt that "serious late changes in the central nervous system" due to radiation "appear to be rare" [6].

Hirsch evaluated the effect of RT on cognitive development by comparing the group of 26 children with PNET with a "control" group of 31 children with astrocytoma (treated only surgically) [19]. Hirsch et al. found a statistically significantly higher proportion of the PNET group had an IQ between 70 and 90, emotional and behavioral disorders, difficulties in spatial orientation, speech, writing, or reading, and academic failures. Conversely, a statistically significant higher proportion of astrocytomas had an $IQ > 90$. Although 31% of the PNET group had an $IQ < 70$ compared with 19% for the astrocytoma group, this difference did not reach statistical significance. Hirsch et al. felt that the deficits in the PNET group were "probably due to the action of ionizing radiations on the vessels and cerebral parenchyma" [19].

Two articles published in the early 1980s refuted the damaging effects of RT. Spunberg et al. concluded that "the developing brain may not be as sensitive to irradiation as previously believed and that children, even under the age of 2, as in our series, tolerate radiotherapy to the brain surprisingly well" [35]. Danoff et al. also found "no apparent correlation between the volume of brain irradiated and mental retardation, as all patients who were mentally defective received local field treatment" [11]. However since 82% of the patients received between 5000 and 5600 rads, Danoff et al. were unable to assess the effect of RT tumor dose on IQ scores.

Conclusions about radiotherapy's cognitive effects in Duffner et al.'s first study were obscured by the use of concurrent methotrexate [12]; clearer conclusions arose from her second study. Duffner et al. found that "the age at the time of cranial irradiation" was a significant factor in "influencing intellectual decline" [13].

Kun and Mulhern found 53% (8/15) of the patients who had received either subtotal supratentorial or cranial

RT had one or more "intellectual delays" [22]. In contrast, only 17% (1/6) of the children with posterior fossa tumors treated with local RT had evidence of intellectual delay. Kun concludes there is "a greater than normal risk for late neuropsychological alterations among children with supratentorial tumors and/or cranial irradiation" [22].

Chin and Maruyama reported only 20% (2/10) of the long-term PNET survivors were deemed mentally deficient. His conclusion was "for patients with medulloblastoma, the incidence of mental or intellectual deficiency occurring after high-dose irradiation has been low" [10]. However, despite using neuropsychological tests, neither summary IQ data nor a comparison between IQ scores and RT tumor dose was presented.

In contrast, Ellenberg et al. [14] divided their 43 study patients into three groups (whole-brain radiation, local tumor irradiation, and no radiotherapy) and analyzed their neuropsychological test results. Four 4 months postoperatively, no difference in mean IQ between the three groups was found. However, over the next 6 months to 4 years the whole-brain RT group showed a statistically significant drop in mean IQ scores (100 to 87.7, $P<0.01$) while the other two groups' mean IQ scores remained stable. Multivariate analysis showed that "the IQ drops were attributable to radiation therapy rather than to tumor site" [14].

Ellenberg et al. then analyzed the combined effect of age and radiation [14]. The two age groups described in the age subsection above (younger and older) were further divided by amount of radiotherapy received (whole brain, local, none). At the 4-month postdiagnosis mark, there was no significant difference between the two age groups. However, at the 1- to 4-year follow-up evaluations, the members of the younger group who had received whole-brain RT had the lowest mean IQ scores and had a statistically significant decline in IQ scores from 90.6 to 70.9 ($P<0.005$). Members of the older age group who received whole-brain RT had a trend toward an IQ decline over time ($0.1>P>0.05$). Children under 5 years old who underwent whole-brain RT exhibited IQ score drops of 20 points or more. The average IQ drop for children between 6 and 8 years old who received whole-brain RT was approximately 10 points. "No consistent IQ declines" were seen in radiated patients older than 9 years old who had RT. There was essentially no change over time for either age group receiving local or no RT. In conclusion, Ellenberg states that "the most potentially devastating treatment in terms of cognitive sequelae for brain tumor patients is radiation therapy" and "the severity of the effects varies inversely with the age of the child."

Bordeaux concluded that radiotherapy was "not associated with acute effects on neuropsychological functions" [7]. However, a brief follow-up time (median 11 months) and small sample size could have been responsible for missing radiation sequelae.

Packer et al.'s 1989 study was a prospective controlled look at the effect of RT on cognition [31]. Compared with baseline testing, the group receiving RT demonstrated a statistically significant decline in multiple IQ scores: FSIQ at year 1 ($P=0.04$), FSIQ at year 2 ($P=0.02$), VIQ at year 2 ($P=0.04$). In addition, WRAT scores exhibited a statistically significant decline between baseline and year 2 in spelling ($P=0.03$) and reading ($P=0.03$). The only parameter associated with this decline was age; younger children exhibited the greatest loss in intelligence. This inverse correlation with age was statistically significant in FSIQ ($P<0.002$) and VIQ ($P<0.001$), but not PIQ.

In the control group of children with cerebellar astrocytomas no intelligence measure showed a statistically significant decline over time. Although the RT group and the control group had similar baseline FSIQ, VIQ, and PIQ, by the end of 2 years a statistically significant difference in FSIQ was found between the RT group (14 point decline) and the control group (1 point gain) ($P=0.05$). The changes in VIQ and PIQ over 2 years in each group did not reach statistical significance. The need for special help in school seen in the RT group was statistically significant. This was different from the control group ($P=0.002$). Despite the small study size, Packer et al. conclude that "whole-brain radiotherapy detrimentally effects cognitive function in children with brain tumors" and this "is especially true in younger patients" [31]. The mechanism for RT-induced damage is currently unclear.

Posttreatment

Postoperative hydrocephalus/need for permanent shunt. Hirsch et al. used postoperative computed axial tomography (CAT) scans of the brain and found "no correlation whatsoever between the IQ and the size of the ventricles" [19]. Ellenberg et al. divided their patients with hydrocephalus into those requiring a shunt and those not requiring a shunt because their hydrocephalus resolved after initial surgery [14]. Despite initial IQ scores in both groups being equivalent, by 4 months the IQ scores of the group requiring shunt placement were statistically significantly different from the IQ scores of the nonshunt group. Ellenberg et al. concluded that the need for a permanent shunt is not a potent predictor of long-term cognitive outcome.

In contrast to the above two studies, Packer et al. found the mean IQ of the shunted patients was 73 compared with the mean IQ of the unshunted patients of 99 ($P<0.05$). In addition, Packer found a statistically significant association between lower performance scores and the need for permanent shunting ($P<0.025$). Packer et al. state: "The reasons for the association between lower intelligence and . . . the need for early cerebrospinal fluid shunting, is less clear" [30].

Complicated postoperative course. Packer et al. found a trend toward association between lower FSIQ scores and either a complicated postoperative course or postoperative infections [30]. Children with a complicated postoperative course had a mean FSIQ of 83 at follow-up compared to a mean FSIQ of 97 for those with an uncomplicated postoperative course. In addition the mean FSIQ for children who suffered postoperative bacterial ventri-

culitis/meningitis was 74 compared to 95 for those who did without. Mulhern reported that the deficits seen in his temporal lobe astrocytoma patients were associated with poor postoperative performance status [27]. However, no clear definition of postoperative performance status was provided, the sample size was small ($n=7$), and no statistical analysis was presented on the data.

Tumor recurrence

Mulhern et al. also reported that the cognitive deficits seen in his temporal lobe astrocytoma patients were associated with tumor recurrence [27]. However, only 1 patient had a tumor recurrence, the overall sample size was small ($n=7$), and no statistical analysis was presented on the data.

Poor seizure control

Another factor Mulhern et al. reported associated with the cognitive deficits was inadequate seizure control. Among the 5 children with postoperative seizure disorders were both children with an IQ <70, all 3 patients with "intellectual deterioration," all 4 with organic brain syndromes, and 2 out of the 3 patients with an IQ between 70 and 90 [27]. However, the overall sample size was small ($n=7$), and no statistical analysis was presented on the data.

Testing interval after treatment

In their first article Kun and Mulhern did not detect a "consistent trend toward deteriorating function in the 10 patients analyzed serially" nor did they find "a higher proportion of subnormal IQ results in patients studied 2 or more years after treatment" [22]. Their second study assessed 18 children serially tested at least twice. At the second evaluation (median 41 months post-RT), 67% (12/18) had FSIQ within 9 points of initial scores (median 22 months post-RT), while 3 improved more than 10 points and 3 dropped more than 10 points. At the third serial evaluation (median 49 months post-RT), 89% (8/9) had stability in their IQ and the other child had improvement in FSIQ scores from 83 to 105. Kun and Mulhern conclude "alterations in intellect are definable and, in large part, stable following treatment" [21]. Limitations in this study included a small sample size and retrospective design.

The third study by Mulhern and Kun found no statistically significant difference in VIQ and CGI between the pre-RT evaluation and the 6-month post-RT evaluation. However, there was a statistically significant difference between the first and second FSIQ ($P<0.01$) and PIQ ($P<0.02$) with both FSIQ and PIQ scores higher at the second assessment [26].

In contrast, both Duffner and Packer have documented statistically significant progressive deterioration in cognitive function as testing interval following treatment increases. Duffner found less than a 1 point decrease in mean IQ 2 years post-RT but a 9 point drop in mean IQ by 3 or more years post-RT [13]. In addition, over the study period a statistically significant proportion of the patients suffered a decrease of >5 IQ points ($P<0.05$). Packer et al. found progressive decline in FSIQ, VIQ, and WRAT in the patients receiving radiation over the 2 years of his study.

Conclusion

Improvements in treatments for childhood brain tumors during the past three decades have led to increasing emphasis by patients, family members, and physicians on the quality of life for these long-term survivors. Until the late 1970s, global descriptions of functional abilities were used to assess cognitive deficits. Although these retrospective uncontrolled studies covered multiple tumor types and various therapeutic modalities, it appeared that from 20% to 40% of long-term survivors had obvious partial disability and $<10\%$ were severely disabled.

The use of formal neuropsychological testing has revealed that the above figures were underestimates of the magnitude of deficits endured by long-term survivors. Formal testing has revealed deficits in not only various intelligence quotients but also visual/perceptual skills, learning abilities, and adaptive behavior. It appears that from 40% to 100% of long-term survivors have some form of cognitive deficit that can be detected by neuropsychological testing.

During the last decade, prospective controlled studies have been conducted to assess the relative contributions of various pretreatment, treatment, and post-treatment variables in the development of cognitive deficits. Certain variables appear to be important (alone or in combination) and related to a high risk of subsequent cognitive deficits, including a younger age at diagnosis, radiotherapy, methotrexate chemotherapy, and tumor location. In addition, more cognitive deficits are detected the larger the time lapse from treatment the testing is done. Surgery and preoperative hydrocephalus do not appear to play a role in the development of cognitive deficits. Some variables, including preoperative obtundation, extent of resection, tumor recurrence, postoperative course, postoperative hydrocephalus and seizures, play as yet unresolved roles.

Overall, the future is encouraging for children stricken with intracranial neoplasms. However, despite the progress in the last decade, future prospective studies are needed to define the role of some variables in the development of cognitive deficits that maximize survival while minimizing cognitive deficits.

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