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Neuropsychological sequelae of the treatment of children with medulloblastoma

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Summary

When a malignant tumor invades the child's cerebellum, the cost of successful treatment is often significant cognitive morbidity. A review of neuropsychological outcome revealed that survivors of childhood medulloblastoma (MB) have long-term deficits in intelligence, memory, language, attention, academic skills, psychosocial function, and a compromised quality of life. These deficits varied with chronological age at tumor diagnosis and/or adjuvant treatment, type and duration of presenting symptoms, tumor extension beyond the cerebellum, a history of adjuvant radiation treatment, and time since treatment. The effects on neuropsychological outcome of other factors, such as post-surgical hydrocephalus, were less clear. To understand the interaction between two factors predictive of outcome, age at diagnosis and time since treatment, we analyzed IQ results for a new sample of 25 surgically-treated and radiated MB survivors, and found that age at diagnosis and time since treatment made separable contributions to intellectual morbidity. PIQ appeared to measure some general effects of diffuse cerebral insult because it varied with chronological age of the child at tumor diagnosis but was relatively constant in magnitude, once established. VIQ, in contrast, was somewhat less sensitive to age at diagnosis in treated MB survivors, but declined with time since treatment. These results are important for understanding the academic attainments and continuing rehabilitation needs of childhood MB survivors, because they suggest that these children progressively fail to assimilate new verbally-based knowledge at a developmentally-appropriate rate.

Medulloblastoma (MB) is a primitive neuroectodermal tumor (PNET) of childhood [1] and accounts for about 25% of primary CNS tumors in the first two decades of life. The posterior fossa is the site of half of all childhood brain tumors [2], and MB is the most common posterior fossa tumor, comprising 39% of posterior fossa tumors [3]. With recent improvements in treatment of this condition, survival after childhood MB has increased dramatically, so now about 60% of children with MB can expect to live five years or longer [4]. An important issue concerns the extent and severity of cognitive morbidity in long-term MB survivors. This morbidity is widespread: Some studies report intellectual deficits, specific skill deficits, or behavioral problems in every MB case studied [5].

The study of neuropsychological morbidity in children treated for brain tumors is often approached using groups heterogeneous for tumor type. This review focuses on studies in which outcome for patients with MB can be ascertained. It includes studies using only MB patients, studies of mixed tumor types in which MB results are reported separately, or studies of childhood tumors that

provide illustrative contexts or relevant contrasts to MB outcome studies. Neuropsychological effects occur in both early and late stages of treatment for childhood MB, but we are particularly concerned here with late effects remaining one year or more post-treatment. After reviewing this material, we present IQ results for a sample of surgically-treated and radiated MB patients from The Hospital for Sick Children (HSC) in relation to two factors – age at diagnosis and treatment, and time since treatment – consistently reported to be associated with long-term neuropsychological morbidity.

Measurement of neuropsychological outcome

Outcome is defined by how it is measured (see [6, 7] for a review of measurement issues in outcome studies of children with brain tumors). The measurement of neuropsychological outcome after childhood MB has ranged from general impressions of outcome to detailed studies of specific cognitive functions.

Functional domains of outcome

Intelligence. Impaired intelligence has long been reported in MB survivors, apparently present in nearly 90% of this population. In 1979, average IQ scores (i.e., 90 or above) were reported in only 11% of MB survivors but in 62% of cerebellar astrocytoma survivors [5]. In a more recent report, all 13 MB survivors had IQ scores below 90 [8].

Specific neuropsychological functions. Neuropsychological studies have identified a range of deficits. One or more forms of cognitive morbidity occur in some 82% of MB survivors [5].

Half of MB survivors have impaired perception and motor function, with the latter being the more impaired. Specific motor deficits in rapid alternating movements and tandem walk occur in half to three-quarters of some samples [8]. Bulbar dysfunction, which involves pseudobulbar palsy or varying combinations of dysarthria, dysphagia, cerebellar dysmetria, truncal ataxia, and mutism, can occur after treatment for MB [9, 10], although the relation with IQ and other cognitive measures is not known.

Children with treated posterior fossa tumors (including MBs) show mild language impairment in auditory comprehension, oral expression, and text-level language skills [11]. They can also have memory deficits [8], which may increase over time [4].

Academic attainments. Academic failure rate is high in MB survivors. Approximately three-quarters have academic failure or reported learning difficulties [5, 8] a rate that is three times higher than that for survivors of cerebellar astrocytomas [5]. Nine years post-treatment, most MB survivors in one sample required special education [12]. Children treated for MB have more problems with arithmetic than with reading or spelling [4, 12, 13].

Psychological function and quality of life. Emotional and behavioral disorders were more common among 28 survivors of MB (93%) than among 31 survivors of cerebellar astrocytomas (59%), although it should be noted that more than half of the latter group were also rated as abnormal on quality of life measures [5]. More recently, it was reported that more than half of the parents of MB survivors reported significant maladaptive behaviors in these children [8]. No specific treatment variables have been associated with measures of psychosocial adjustment [12].

In early studies of MB survivors, gross quality of life measures did not predict psychometric or educational outcome [5]. Because neuropsychological measures are themselves indicators of quality of life, a more theoretically-grounded assessment of health-related quality of life and psychosocial skills will be important in new outcome studies of MB survivors, together with analyses of their relation to neuropsychological function [6, 7].

Reference groups used to establish outcome

In the literature on MB and neuropsychological outcome, various pediatric reference groups have been used to establish outcome. These include published norms for age peers [8], siblings or cousins

[13, 14], and children with posterior fossa tumors not requiring radiation or chemotherapy [5, 15]. To date, we have found no published comparison of neuropsychological function in MB survivors and a normally-developing control group of age peers.

Explicit comparison between children and adults with MB might prove instructive with respect to anatomical locus of tumor, the presence of hydrocephalus, and age at diagnosis and treatment. MB is rare in adults, accounting for only 1% of adult brain tumors [16]. One-third of adult MBs present as vermian tumors [17], whereas 93% of childhood MBs are located in the vermis [18]. Hydrocephalus is present in less than half of adults with MB, but occurs in 85–100% of children with MB [17]. Age has a profound effect on outcome in children with MB but no effect on prognosis for cerebellar MBs in adulthood [19].

Determinants of neuropsychological outcome after MB in childhood

Studies of cognitive morbidity have explored how neuropsychological function and quality of life are related to several variables. These include factors in the child, features of the tumor, factors associated with primary treatment, features of the adjuvant treatments of radiation and chemotherapy, the time since treatment, and the interactions among these factors.

Factors in the child

Chronological age at tumor diagnosis and/or adjuvant treatment. In the studies reviewed in this section, 'age at diagnosis' is used to indicate both age at diagnosis and age at adjuvant treatment with radiation and/or chemotherapy. Prospective studies of children having various types of brain tumors have shown no IQ differences at time of diagnosis between younger and older patients [20, 21]. However, a younger age at MB diagnosis has been consistently associated with greater neuropsychological dysfunction later on [22–24]. An older age at diagnosis even seems to be protective. A boy who was diagnosed with MB at age 18 had a neuropsychological profile similar to that of his identical twin more than three years after treatment [25].

Diagnosis of MB before the age of 3 is associated with significant intellectual morbidity [8, 26]. In 11 five-year survivors of MB treated before 3 years of age, 55% had IQ scores under 80 [27].

Recent data suggest that diagnosis after age 3 may also compromise intellectual function. In the Johnson *et al.* [8] study, none of the 13 MB patients had an IQ over 90, and IQs were below normal both for children diagnosed under age 3 (Mean IQ = 65) and those diagnosed over age 3 (Mean IQ = 80). Accordingly, 6–7 [4, 28] and 8 [13] have also been identified as ages below which MB diagnosis is associated with intellectual deficit.

The rate of IQ decline, not just IQ level at one post-treatment time point, also appears related to an earlier age at diagnosis. Children younger at the time of MB diagnosis and treatment show a greater decline in IQ scores over a two-year period than do children who are older [4].

The relation between age at diagnosis and particular cognitive abilities is less well studied than that between age at diagnosis and IQ. There is a tendency towards lower academic achievement in MB survivors treated at an earlier age [8]. In a sample of 12 MB patients and 6 ependymoma patients, a young age at diagnosis was related to greater frequency of special education services and poorer academic achievement [12].

Type and duration of presenting symptoms. Obtundation at the time of diagnosis, other types of mental status changes, and ocular motor deficits are each associated with low post-treatment IQ scores [29]. Shorter duration of symptoms is associated with poorer neuropsychological outcome in these children [29], possibly related to more severe or abrupt increases in intracranial pressure.

Features of the tumor

Tumor location. MBs are located in the cerebellar vermis in nearly all pediatric cases, although outcome is better with a lateral cerebellar localization

[30]. Extension of the tumor to the brain stem, which occurs in some 32% of cases [18], appears related to lower IQ [5]. In the studies reporting this variable, there is no correlation between tumor staging and IQ [10].

Factors associated with primary treatment

Extent of tumor resection. Probability of survival is improved with total MB resection [31]. Neuropsychological morbidity has not been often studied in relation to extent of tumor resection, although one study found that IQ and academic achievement in children treated for MB were unrelated to whether tumor resection was gross total or partial [8].

Residual tumor. It is not known whether the factors that reduce mortality are those that affect neuropsychological function. The amount of tumor remaining after surgery, rather than the size of the tumor or the structures invaded by tumor at time of surgery (T stage), may be prognostic of long-term survival [32]. Whether this is also prognostic of short- or long-term neuropsychological morbidity has not been studied.

Peri-operative factors. Some evidence has related peri-operative factors to neuropsychological outcome. Packer *et al.* [4] found no association between IQ and post-operative complications, which included meningitis, hemorrhage, or prolonged obtundation, in children treated for MB. In contrast, Kao *et al.* [10] reported that peri-operative factors, which included neurological deficits, meningitis, subdural fluid collections, and repeat craniotomy, were strongly associated with declines in IQ scores and were more predictive of IQ than even age at treatment.

Hydrocephalus. Hydrocephalus is a significant complication of infratentorial brain tumors [33]. Somewhere between 8% and 35% of children with posterior fossa tumors will require a shunt [9]. The evidence relating hydrocephalus to outcome is unclear. There is no correlation between IQ and either post-operative ventricular dilation [5] or non-emergent shunt placement [10]. Conflicting results have been reported concerning the effects of shunt history on neuropsychological function. One study [29] reported higher IQ scores in non-shunted patients, but another [8] showed that motor dexterity and speed, intelligence, and academic achievement were all higher in shunted MB survivors.

Endocrine dysfunction. Growth hormone deficiency, short stature, and compensated hypothyroidism are fairly common in treated MB survivors due to the inclusion of the pituitary in the radiation field [5, 18]. No relation has been documented between endocrine sequelae and cognitive or behavioral problems [5].

Features of adjuvant treatment

Cranial radiation and chemotherapy are adjuncts to surgery for children with MB. These forms of adjuvant therapy entail a risk of cognitive morbidity, the extent of which is only now becoming apparent as children are assessed over longer periods of survival.

History of radiation treatment and surgery. Children treated with craniospinal radiation, whatever their age, have lower IQ scores (by 12–14 points) than children who are not radiated [6]. MB survivors treated with radiation have lower IQ scores than do non-radiated survivors of cerebellar astrocytomas [5], or than sibling controls [13]. It is clinically important that deterioration in IQ over time occurs in children radiated for MB but apparently not in non-radiated survivors of cerebellar astrocytomas [4].

Radiation dose-response relationships. Studies of long-term MB survivors have found no association between radiation dose and neuropsychological function [8]. A 1992 overview [6] reported that no studies had been found relating radiation dose to IQ decrements. In a group of mixed childhood brain tumors, higher radiation doses produce poorer attention, regardless of age at radiation [34]. An absence of radiation dose effects on IQ differences with siblings has been reported [13]. No correlation

has been found between dose of whole brain radiation and academic, vocational, or psychosocial function for children with malignant posterior fossa tumors [12].

The absence of a dose-response relationship in these studies may reflect a restriction in the range of doses studied. A broader range of radiation doses have been examined in studies comparing radiation effects in children with leukemia and children with MB; here, a dose effect has been reported such that a whole-brain dose of 36 Gy produces a greater decline in IQ over time than does a whole-brain dose of either 24 Gy or 18 Gy [35].

Chemotherapy. For treated MB survivors, there is no correlation between the use of adjuvant chemotherapy and either IQ, academic attainments, vocational function, or psychosocial adjustment [10, 12, 36].

Time since treatment

As early as 1976, it was suggested that mental handicap might be progressive after treatment for malignant brain tumors of childhood, and also that MB survivors might suffer a long-term plateau of mental development [37]. Later research has supported the claim of progressive intellectual deterioration in radiated MB survivors [15, 27, 29, 38, 39]. Forty-two percent of radiated MB survivors had intellectual deficits at 5 years post-treatment and 80% showed these deficits at 10 years post-treatment [27]. Declines in IQ were documented between baseline and the second year of follow-up, with no further decline seen between the second and fourth year [36]; very long-term outcome in this cohort is yet to be determined.

For specific neuropsychological functions, time since treatment effects are complex. In contrast to IQ, fine motor skills were impaired at diagnosis and thereafter, but no progressive decline was noted over a 4-year period in a cohort of 19 children treated with radiation for malignant posterior fossa tumors, including 15 with MB [4]. Memory deficits have been reported to increase with follow-up time [4].

A retrospective study of 13 MB patients reported no differences in cognitive and academic measures between patients who were less than 10 years since treatment and those treated more than 10 years earlier [8]. In this retrospective study, it was not reported whether significant cognitive declines had occurred during the first 10 post-treatment years.

Social and emotional difficulties seem to follow a pattern of increasing frequency with longer time since diagnosis and treatment. Disorders of social-emotional functioning were evident in 47% of radiated MB patients after 5 years, but in 78% after 10 years [27]. Quality of life was also related to a longer time since diagnosis in another sample of MB survivors [12], such that the longer the interval, the poorer the psychosocial adjustment and family function.

Interactions among variables affecting outcome

The variables associated with childhood MB and its treatment do not operate in isolation from each other. For example, age at diagnosis may be related to the aggressiveness of the tumor, with more aggressive tumors being more common in younger children [22]. Tumor surgery may also be more complex in younger children, and the extent of tumor resection is important in decisions about adjuvant therapy. Peri-operative complications, associated in some samples with lowered IQ [10], are more prevalent in younger children and are correlated with poorer neuropsychological outcome [28]. The interactive effects of the various tumor-related variables on neuropsychological function (rather than on survival) remain to be fully understood. For example, particular variables such as tumor aggressiveness may affect survival, but it is less clear how the interaction among tumor aggressiveness, age at diagnosis, and surgical complications impact on neuropsychological outcome.

Multimodal treatments. In children with brain tumors diagnosed before the age of 2 (40% in the posterior fossa), surviving patients treated with surgery and chemotherapy have better-preserved intelligence than do patients treated with surgery and ra-

diation [40]. Similar findings have been reported in other studies [41].

Age at diagnosis and time since treatment. The relation between age at diagnosis and time since treatment is of particular interest in understanding the neuropsychological effects of MB and its treatment. Age at diagnosis is often correlated with time since treatment, itself a risk factor for neuropsychological deficits. For example, Silverman *et al.* [13] noted a tendency for greater loss of IQ in relation to siblings in children tested 5 or more years post-treatment compared to children treated more recently than 5 years, but these children were also younger at the time of diagnosis.

The HSC MB sample: A study of the interaction between age at diagnosis and time since treatment

While age at diagnosis and time since treatment each affect neuropsychological outcome in survivors of childhood brain tumors, the interaction of these factors is not fully understood. We could not find any published studies that formally analyzed the joint effects of age at diagnosis and time since treatment in MB survivors.

To explore the separate and conjoint effects of age and time on cognitive morbidity after treatment for MB, we have analyzed IQ data on 25 MB patients from our clinical and research files at HSC. The sample of 7 females and 18 males ranged in age from 6.01 to 18.09 years. The inclusion criterion was a history of MB treated with both surgery and radiation; the exclusion criterion was no tumor recurrence prior to the post-treatment IQ assessment. Seven of the 25 patients had been treated with chemotherapy in addition to radiation. Sex and chemotherapy were not significant factors in any of the analyses conducted, so the data are not presented separately according to these varibles. Results are presented in Table 1, which shows means, standard deviations, and ranges for age at diagnosis, the number of years between diagnosis and IQ testing, and Full Scale (FSIQ), Verbal (VIQ) and Performance IQ (PIQ) from the age-appropriate Wechsler IQ test.

As a group, the mean FSIQ, VIQ, and PIQ were more than one standard deviation below the normative sample for the Wechsler series. These differ-

Table 1. Age at diagnosis, time since treatment, and IQ test scores

Group	Age at diagnosis	Time since treatment	Wechsler Intelligence Scale Scores		
			FSIQ	VIQ	PIQ
Full Group (n = 25)					
Mean	5.53	6.16	78.4	85.44	74.32
SD	3.24	4.70	14.14	14.91	13.99
Range	0.27–12.19	0.82–15.69	53–107	58–107	45–106
Subgroups diagnosed at 0–3 yr (n = 8)					
Mean	1.86	9.35	67.5	74.38	65.38
SD	1.05	4.97	13.21	14.87	10.04
Range	0.27–2.82	2.88–15.69	53–86	58–92	54–82
4–6 yr (n = 9)					
Mean	5.52	4.13	82.75	90.38	77.75
SD	0.84	4.87	10.99	14.89	10.06
Range	4.43–6.67	0.82–13.87	64–90	68–105	59–82
≥ 7 yr (n = 8)					
Mean	9.16	4.51	85.63	93.75	78.88
SD	1.9	2.62	12.78	7.83	17.88
Range	7.02–12.19	1.63–8.74	64–107	83–107	45–106

Note: IQ scores are from the age-appropriate Wechsler scale [54–58].

ences between the MB patients and the normative sample were significant for all measures (FSIQ: $t[24] = 7.64$, $p < 0.0005$; VIQ: $t[24] = 4.86$, $p < 0.005$; PIQ: $t[24] = 9.18$, $p < 0.0001$). A significant number of our sample, 21 of 25, had lower PIQ than VIQ ($\chi^2[1] = 11.56$, $p < 0.001$), and there was a reliable difference between group means for VIQ and PIQ ($t[24] = 4.5$, $p < 0.0005$).

To facilitate comparison of our sample with those in the published literature, we grouped the patients into three age-at-diagnosis categories (below age 4; age 4–6; age 7 and over) and compared IQ scores using one-way ANOVAs. Group differences were found for FSIQ ($F[2, 22] = 4.83$, $p < 0.02$) and VIQ ($F[2, 22] = 4.69$, $p < 0.03$), but not for PIQ. Post hoc analyses using the Tukey-HSD procedure showed that the significant differences were those between the youngest and the oldest groups. However, ANOVAs for group membership with time since treatment as a covariate demonstrated that it was time since treatment rather than age at diagnosis that was producing the group differences in FSIQ and VIQ scores. In the ANOVAs, membership in the age at diagnosis groups was no longer significant, but the covariate, time since treatment, emerged as significant (FSIQ: $F[1, 21] = 10.20$, $p < 0.005$; VIQ: $F[1, 21] = 16.42$, $p < 0.002$).

The effect of age at diagnosis and time since treatment on IQ measures was analyzed further using stepwise multiple regressions. Age at diagnosis and time since treatment, although negatively correlated ($r = -0.46$, $p < 0.03$), were found to make measurably separate contributions to IQ scores.

For VIQ, time since diagnosis accounted for 40% of the variability in the sample ($r^2 = 0.40$; $F[1, 23] = 15.38$; $p < 0.0008$); adding age at diagnosis explained a further 9% of the variance, which was not a statistically significant improvement in the regression model. For PIQ, the best model included only age at diagnosis, accounting for 18% of the variability in scores ($r^2 = 0.18$; $F[1, 23] = 4.91$; $p < 0.04$). Adding time since diagnosis to this model explained no further variance. Because VIQ and PIQ had different significant predictors, a regression model of their composite, FSIQ, could not reasonably be interpreted.

The results show that the impairment of PIQ is related primarily to chronological age at the time of tumor diagnosis, and appears constant in magnitude after the tumor is treated. In contrast, the impairment of VIQ increased with time elapsed since treatment, being less dependent on the stage of development at which the tumor was diagnosed.

Discussion

The cerebellum occupies only one tenth of the brain, yet contains over half of its neurons [42]. The role of the cerebellum in modulating and integrating motor activities has long been acknowledged [43, 44]. Recent neuroanatomical, neuropsychological, and neuroimaging studies have proposed a broader role for the cerebellum in general timing functions, and in higher cognitive functions including language [45–47]. In this broader role, a disruption of the timing and cognitive mechanisms of the cerebellum would have significant consequences for the development of intellectual functions.

A cerebellar location for a childhood brain tumor might therefore be expected to have more than just motor morbidity. The literature shows that childhood brain tumors below the tentorium bring a risk of cognitive morbidity, affecting a variety of higher cognitive functions. While MBs have the greater risk of neuropsychological impairment, non-malignant cerebellar tumors are also associated with motor, intellectual, and specific cognitive deficits [6, 15].

In our review of the literature, chronological age at diagnosis and treatment predicted long-term neuropsychological morbidity. Intellectual deficits appear highly likely when MB diagnosis occurs in the preschool and kindergarten period. Neuropsychological morbidity is reduced as age at diagnosis and treatment increases, such that radiation after age 7 or 8 is associated with a lesser degree of risk.

Chronological age may match imperfectly with both cognitive developmental stage and stage of brain maturation, and thereby provide oblique information about specific processes mediating neurobehavioral risk. It would be informative to group MB children not only by chronological age, but also by theoretical or empirically determined develop-

mental stages or critical periods [7]. Advances in neuroimaging may offer a more direct index of brain maturation, and so identify the optimal time for treatment in terms of specific markers of brain development.

Early insults to the developing brain have consequences that can be fully appreciated only later in development [48, 49], which underscores the need for long-term tracking of neuropsychological functions. For practical reasons, most long-term follow-up studies of MB survivors have been retrospective in design. Future studies might involve serial longitudinal testing with individual growth curve analyses [50] that study group outcomes but that also allow individual differences in developmental trajectories to be analyzed in relation to time since treatment.

Neuropsychological outcome after childhood MB is determined by the conjoint effects of several variables [6, 7]. Some authors have suggested that the focal effects of the tumor carry a decreased risk for younger subjects, while more generalized insults to the brain, such as those induced by radiation, would impart an elevated risk for the same age group [7]. To the extent that particular features of an MB child's medical history might carry different valences for long-term cognitive function, it becomes important to study the interactions among tumor-related variables.

Age at diagnosis and time since treatment are each predictive of cognitive status in survivors of childhood MB. It has been suggested that increased cognitive morbidity in younger children may be confounded by longer intervals between diagnosis and test, the effect of which would be to overestimate the impact of age at diagnosis on outcome [7]. This could be the case, for example, in retrospective studies of pediatric populations with an upper age limit of 18 at time of study, where individuals with the longest time since treatment would be those who were youngest at diagnosis. The task, then, is to evaluate how both age and time variables affect outcome, when these variables are analyzed conjointly for the same subjects.

In our new series of 25 MB survivors, age at diagnosis and time since treatment were correlated, such that a younger age at diagnosis and treatment was associated with a longer time since treatment. Nevertheless, age and time made separable contributions to intellectual morbidity, and the effects of MB and its treatment on intelligence were both general and specific.

The processing of visuo-spatial information under time constraints, measured by PIQ, is impaired for most MB patients, and this impairment is more severe with a younger age at diagnosis. In addition, individuals treated with radiation have a lower PIQ than VIQ. These effects parallel reports of slowed information processing and psychomotor speed after diffuse or multifocal brain insults such as head injury [51]. In contrast, the ability to accrue a complex knowledge base, to add to vocabulary and to social and academic knowledge through experience, as measured by VIQ, is most clearly related to time since treatment, such that a longer time since treatment is associated with lowered verbal intelligence.

Each IQ scale appears to measure different types of processes associated with brain damage. PIQ reveals some general effects of diffuse cerebral insult that vary with the chronological age of the child at brain insult but which are relatively constant in magnitude over survival time. On the other hand, VIQ is less sensitive to onset age in treated MB survivors, but continues to decline for several years after treatment.

Incremental declines in IQ scores might come about from deteriorating brain function, inability to make age-appropriate gains in skill and knowledge, or both. Children who have received central nervous system radiation show progressive pathological brain changes [52] as well as increasing academic difficulties. If the observed declines were related solely to progressive brain pathology, a time-bound deterioration of both verbal and non-verbal intelligence would be predicted. Instead, only verbal intelligence declines with time since treatment. Although the effects of progressive neuropathology cannot be ruled out in these effects, it appears that the failure to accrue knowledge may be more a consequence of a time-delimited brain pathology interacting with environmental factors over time. The result is that the VIQ scores of MB survivors become lower with increasing time since treatment.

This need not entail any cognitive decline; it means only that childhood MB survivors increase their verbal capacities less than do normally-developing children over the same time span.

Several questions remain unanswered about the long-term neuropsychological effects of childhood MB. One concerns the separate effects on outcome of age at surgery and age at radiation. Another concerns the specificity for MB of age at diagnosis and time since treatment effects.

In published studies of MB, adjuvant treatment is instituted shortly after tumor diagnosis. In the studies reviewed in this paper, 'age at diagnosis' was used as a marker for both age at diagnosis and age at adjuvant treatment. As data are accumulated about the effects on cognitive development of the current practice of delaying radiation in younger children diagnosed with MB, it will be possible to decompose the separate effects of these two age variables and thus address issues about whether PIQ effects stem from age at surgery/chemotherapy or age at radiation.

It is not clear at present whether age at diagnosis and time since treatment effects are specific to MB, or whether, instead, they occur after any form of cerebellar tumor. Work in progress comparing our MB series with a series of survivors of cerebellar astrocytomas is designed to address this question. Recently, time since treatment effects were shown to differ in children receiving whole brain vs. posterior fossa radiation [53].

In summary, a treated malignant tumor that arises in the child's cerebellum is likely to be associated with a significant degree of cognitive morbidity in which the rate of cognitive development is slowed and the final level of cognitive development is attenuated. While much remains to be learned about the cognitive morbidity of childhood MB, it does appear that the child at greatest risk for serious and persisting neuropsychological deficits after treatment for MB is the one who is younger at diagnosis and is several years post-treatment. The motor slowing and losses of psychomotor speed are obvious deficits and ones that are likely to receive attention; however, verbal intelligence remains the best predictor of academic achievement. It is the inability to accrue new knowledge, reflected by the decline in VIQ over time, that is likely to limit the neuropsychological development and academic attainments of survivors of childhood MB. Clearly, it will be important to determine whether neurocognitive rehabilitation instituted shortly after the completion of treatment can ameliorate the consequences of progressive intellectual deficits in MB survivors.

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