

Neuropsychological resiliency after treatment for advanced stage neuroblastoma

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Summary:

The purpose of this study was to describe the neuropsychological functioning of survivors of advanced stage neuroblastoma. In all, 16 survivors, diagnosed at a median of 2.8 years, who had received intensive chemotherapy and surgical treatments, were identified; 11 had received myeloablative consolidation therapy, eight with total body irradiation (TBI). All patients were evaluated with a neuropsychological assessment battery at a median age of 8.8 years. Analyses included comparison of the performances of the TBI group vs the no-TBI group; determination of whether the proportion of individuals with impaired or superior performance on each measure exceeded normative expectations; and performance indexes reflecting patterns of performance. Results indicate no significant deleterious impact of TBI and/or presence or absence of myeloablative therapy on neurocognitive and neurobehavioral functioning. For this cohort, resilience to neuropsychological vulnerability was observed, which included the emergence of a profile of full-scale IQ, verbal IQ, and mathematical achievement well above average expectations. We concluded that the results document a lack of neuropsychological morbidity among this cohort of survivors of advanced stage neuroblastoma, regardless of the inclusion of TBI. Moreover, a striking pattern of excellent neurocognitive functioning with intact neurobehavioral functioning was observed.

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Neuroblastoma is the most common extracranial solid tumor of childhood, accounting for one in every 12 new cancer

diagnoses in children under 15 years of age in the US;¹ 90% of cases diagnosed before the age of 5 years² with a median age at diagnosis of 2 years. Children of any age with localized neuroblastoma and infants with advanced favorable biology disease have a high likelihood of long-term, disease-free survival.³ However, patients diagnosed older than a year of age with advanced stage disease (Stage 4) or regional disease with poor risk biologic features (Stage 3) have a poor prognosis and require aggressive combined modality therapy with intensive chemotherapy, surgical resection of the primary tumor (usually located in the abdomen or thorax), radiation to that site, and, often, consolidative therapy with a stem-cell-supported myeloablative regimen. Although this aggressive approach has resulted in improvements in long-term survival rates,^{4–7} there is concern that children receiving this very aggressive therapy during a period of rapid brain development might have neuropsychological deficits resulting from their therapy, particularly if the myeloablative consolidative therapy includes total body irradiation (TBI) which includes the brain.

The specific impact of bone marrow transplant (BMT) and TBI on the neuropsychological functioning of children treated for advanced neuroblastomas has not been previously studied, perhaps due to low cure rates and the very young age of the patients treated. However, the impact of treatment with BMT for various pediatric conditions including aplastic anemia and leukemia on neurocognitive and neurobehavioral functioning has been investigated.^{8–13} Findings have been mixed, with reports of stable cognitive and neuropsychological functioning, normal somatic growth and normal development of intelligence, language, perception, and motor coordination at different time intervals post-treatment^{14–17} in direct contrast to conflicting reports of declines in IQ and adaptive behavior, general developmental delay, motor deficits, and varying degrees of perceptual and cognitive problems at various intervals post treatment.^{18–20} Therapies which precede BMT and TBI in patients with leukemia, such as intrathecal therapies and cranial radiation, make it difficult to assess the isolated effects of BMT and TBI on neuropsychological functioning of survivors. In neuroblastoma patients, who rarely receive pre-transplant therapies known to effect neurocognitive function, the specific impact of BMT and TBI is not well studied. For this reason, we sought to identify survivors of

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advanced stage neuroblastoma who had reached an age that would be appropriate for neuropsychological testing (at least age 6), and to investigate their neurocognitive and psychological functioning.

We describe here the neuropsychological functioning of a group of 16 survivors of advanced stage neuroblastoma, with specific interest in documenting the impact of TBI on neurocognitive and neurobehavioral functioning and in describing the neuropsychological functioning of these patients.

Methods

Patient recruitment

Patient databases were queried for patients who met the following criteria: diagnosis of 'high-risk' neuroblastoma, at least 1 year from treatment completion, and current age between 6 years–0 months and 15 years–11 months. We identified 28 eligible patients meeting these criteria, and received permission from the treating physician to contact the patient's parents by mail, with follow-up phone calls from one of the investigators (SC). Using this recruitment scheme, 16 agreed to participate, two declined, six were lost to follow-up, and four did not respond. Reason for declining participation was lack of interest in the study. Non-participants were similar to participants in median age at diagnosis, median current age, and median length of time between diagnosis and current age.

Demographics and treatment characteristics

Specific demographic and treatment characteristics for each of the 16 patients in this cohort are presented in Table 1.

All of the patients in this cohort had undergone resection of their primary tumors at some point during their chemotherapy. No patient had a history of craniotomy, primary tumor, or known metastatic site in the brain parenchyma. Five of the nine patients with metastatic disease had skull metastases, but only one patient (#2) had received focal external beam radiotherapy to the site (left parietal bone). Only one patient (#1) had opsoclonus–myoclonus syndrome as a presenting symptom of neuroblastoma.

The median age of diagnosis for this cohort was 2.8 years (range = 1 year–1 month to 10 years–4 months), median age at time of assessment was 8.8 years (range = 6.1–15.11 years), median elapsed time between diagnosis and assessment was 6 years (range = 1.6–13 years) and median educational placement was third grade (range = kindergarten through 11th grade). All of the parents had earned a high-school education and 44% of both mothers and fathers had earned advanced degrees; more specific employment or socio-economic status information was not available.

Assessment procedure

Neuropsychological assessments were conducted in 1 day and assessed five neurocognitive domains: intellectual functioning,²¹ language learning and memory,^{22,23} visuo-spatial learning and memory,^{24,25} motor functioning and achievement²⁶ as well as two neurobehavioral domains (general behavior²⁷ and self-concept²⁸).

Informed consent for participation in this study was signed by the parent on the day of the scheduled assessment. This protocol was approved by the Institutional Review Boards at both Children's Hospital, Boston

Table 1 Patient demographics and treatment characteristics

ID#/ Sex	Age at tx (years)	Stage & Induction tx	Transplant conditioning	Autologous transplant #1	Autologous transplant #2	TBI dose	Age/grade at assmt	Services	Hearing status
1/F	2	4 – POG	Yes	VP16/Cytox/Carbo	TBI/melphalan	1200 cG	6y-1m/k	ST,PT,OT,T	WNL
2/F	3	4 – POG	Yes	VP16/Cytox/Carbo	TBI/melphalan	1200 cG	8y-6m/3rd	N	HA
3/F	3	4 – POG	Yes	VP16/Cytox/Carbo	TBI/melphalan	1200 cG	7y-2m/1st	N	HA
4/F	1	4 – POG	Yes	VP16/Cytox/Carbo	TBI/melphalan	1200 cG	7y-4m/1st	ST	HFHL
5/M	1	4 – POG	Yes	VP16/Cytox/Carbo	N	N	6y-5m/k	HN	HFHL
6/F	2	4 – POG	Yes	VP16/Cytox/Carbo	TBI/melphalan	1200 cG	7y-10m/2nd	N	WNL
7/F	3	3 – HDP	Yes	VP16/Cytox/Carbo	N	N	11y-6m/5th	N	HFHL
8/M	4	4 – POG	Yes	VP16/Cytox/Carbo	TBI/melphalan	1200 cG	6y-5m/1st	N	HFHL
9/F	10	3 – POG	Yes	VP16/Cytox/Carbo	TBI/melphalan	1200 cG	13y-3m/7th	N	HA
10/F	3	4 – POG	Yes	VP16/Cytox/Carbo	TBI/melphalan	1200 cG	9y-1m/3rd	N	WNL
11/F	4	3 – MADDOC	No	N	N	N	14y-4m/9th	N	HFHL
12/F	2	3 – MADDOC	No	N	N	N	15y-11m/11th	N	WNL
13/F	1	4 – POG	No	N	N	N	7y-3m/1st	ST,OT	HFHL
14/M	2	3 – HDP	Yes	VP16/Cytox/Carbo	N	N	10y-7m/5th	N	HFHL
15/F	1	3 – MADDOC	No	N	N	N	14y-10m/9th	N	HFHL
16/M	2	3 – MADDOC	No	N	N	N	13y-3m/7th	N	WNL

y = years; m = months.

POG = alternating cycles of cisplatin/VP16; Adria/VCR/Cytoxan; Carboplatin/VP16; Ifosfamide/VP16.

MADDOC = nitrogen mustard, Adria, DTIC, Cisplatin, VCR, Cytoxan.

HDP = HDP/CTX + ICE = platinum/cytoxan × 2, followed by ifosfamide/carboplatin/etoposide.

N = none received.

Services at the time of assessment: All patients were enrolled in a regular classroom setting; some were receiving specific services (for speech therapy (ST), physical therapy (PT), occupational therapy (OT), or tutoring (T)) or specific accommodations (for hearing needs (HN)).

Hearing status at time of assessment: within normal limits (WNL); hearing aid user (HA); high-frequency hearing loss (HFHL).

and Dana-Farber Cancer Institute (DFCI). Parents were provided with oral feedback and written reports of the child's performance, prepared by one of the investigators (SC).

Statistical methods

For each measure, raw scores were converted to age-appropriate scaled or standardized scores using published norms.^{21–28} ANOVAs were used to compare the performances of those patients who had received TBI with the performances of those patients who did not receive TBI. In addition, the difference between verbal IQ and performance IQ scores was evaluated by paired *t*-test. A discrepancy of 1 standard deviation (s.d.) or greater was considered significant for purposes of non-parametric analyses.

Furthermore, descriptive statistics were generated for the neuropsychological measures. Each score was coded as either 'average' (within 1 s.d. from the mean), 'below average' (1 s.d. or more below the mean) or 'above average' (1 s.d. or greater above the mean). Binomial distribution analyses were conducted to assess whether the proportion of patients showing 'below average' or 'above average' performance exceeded normative expectations.

Lastly, to assess whether group findings of specific performance patterns were attributable to the performance of a few children across multiple areas or reflected the performance of the cohort as a whole, two indexes were calculated for each child, one reflecting impaired ('below average') performance and another reflecting superior ('above average') performance.

Results

Risk factor analysis

Since the major risk factor for neurocognitive dysfunction in this cohort was hypothesized to be TBI, we analyzed the results of neuropsychological testing by grouping patients into two groups, those with and those without exposure to TBI. There was no difference between the two groups in age at diagnosis, age at neuropsychological testing, academic placement or gender. TBI-treated patients were more likely to have Stage 4 disease. The two groups were very similar in their performances on all of the neurocognitive and neurobehavioral measures (see Table 2). Since there were no differences between the two groups on any measures, they were combined into one cohort for subsequent analyses.

Analysis of the cohort

Mean, median and ranges of IQ and achievement scores for the entire cohort are presented in Table 2. Although the proportion of 'below average' performances on each of the neuropsychological measures was no more frequent than expected based on population norms, there were significant findings in terms of 'above average' performances, specifically in the cognitive domain of Verbal IQ ($P < 0.01$) and Full Scale IQ ($P < 0.01$). Significantly, 50% of this cohort exhibited Verbal IQs and 44% exhibited Full-Scale IQs that were at least 1 s.d. *above* the population. In addition, 45.5% of this cohort exhibited a Verbal IQ which was at least 1 s.d. greater than their Performance IQ ($P < 0.05$). Furthermore, performance on specific verbal processing subtests

Table 2 IQ and achievement performance distribution

	Mean	Median	Range	Comments
<i>For cohort as a whole</i>				
Verbal IQ	113	114.5	88–128	50%* of pts with above average performance
Performance IQ	107	109	83–130	25% of pts with above average performance
Full-Scale IQ	111	113.5	89–133	44%* of pts with above average performance
Reading	108	107.5	85–133	19% of pts with above average performance
Math	108	109.5	90–123	38%** of pts with above average performance
Spelling	103	101.5	85–123	19% of pts with above average performance
<i>For TBI group</i>				
Verbal IQ	113	118	88–124	
Performance IQ	105	107	89–121	
Full-Scale IQ	111	115	89–121	
Reading	110	109	85–133	
Math	104	106	90–118	
Spelling	104	98	85–123	
<i>For no-TBI group</i>				
Verbal IQ	114	115	97–128	
Performance IQ	109	110.5	83–130	
Full-Scale IQ	112	112.5	96–133	
Reading	104	106	91–115	
Math	110	112	91–123	
Spelling	103	101.5	89–122	

*% NBL survivors with scores greater than 1 s.d. above mean is significant ($P < 0.01$).

**% NBL survivors with scores greater than 1 s.d. above mean is significant ($P < 0.05$).

NB: Since the TBI and no-TBI groups were very similar, the proportion of patients in the above average range is only given for the cohort as a whole.

was striking. For example, 37.5% of the cohort exhibited above average performance on the Information subtest ($P < 0.05$), 56.3% exhibited above average performance on the Similarities subtest ($P < 0.01$), 50% exhibited above average performance on the Vocabulary subtest ($P < 0.01$), 43.5% exhibited above average performance on the Comprehension subtest ($P < 0.01$), and 37.5% exhibited above average performance on the Digit Span subtest ($P < 0.05$).

Performance on nonverbal processing subtests, although not as striking as the language processing subtests, was nevertheless remarkable. For example, 50% exhibited above average performance on the Coding subtest ($P < 0.01$) and 37.5% exhibited above average performance on the Block Design subtest ($P < 0.05$). Performances on tasks assessing memory and learning in language and visuo-spatial domains were all solidly within average expectations, as was performance on tasks in the motor domain. In terms of achievement skills, basic reading and spelling skills were solidly average. Mathematical reasoning skills, however, were particularly strong, as evidenced by 37.5% of this cohort ($P < 0.05$) scoring at least 1 s.d. above average expectations.

Performance on tasks assessing behavioral functioning and self-concept within the neurobehavioral domain indicated no deficits in any of the three domains of self-concept (academic, physical, social) nor in parental report of the child's behavioral functioning. The reports of self-concept and behavioral functioning were solidly within the average range for all in this cohort.

Index scores

The superior performance index reflected an elevated level of performance for the group as a whole. Of the 16 patients, 15 (94%) exhibited superior performance on at least one measure and 11 (69%) exhibited superior performance on five or more measures. In contrast, the impairment index score was more a reflection of the performance of a few individuals rather than the cohort as a whole. Specifically, 44% (seven of the 16 patients) did not exhibit impaired performance on any of the tasks and 19% (including pt #1 who presented with opsoclonus-myoclonus, and pts #13 and #16, neither of whom received transplant or TBI) exhibited poor performance on five or more measures.

Discussion

The primary purpose of this study was to describe the long-term neuropsychological outcomes of children who received intensive therapy for advanced stage neuroblastoma. We sought to determine whether there were any differences in neurocognitive or neurobehavioral functioning between pediatric survivors of advanced stage neuroblastoma who had been treated with TBI in comparison to those who had been treated without TBI. Our primary finding from this cohort of patients is that there is no neurocognitive morbidity nor any neurobehavioral vulnerabilities that can be documented in those treated with TBI when compared to those treated without TBI. A rather un-

expected finding, however, was the emergence of a neuropsychological profile of specific strengths for the entire cohort.

Our findings supplement the current pediatric oncology literature in several ways. In studying neuroblastoma survivors, we had an opportunity to more explicitly assess any potential impact of TBI on neuropsychological functioning without introducing any additional morbidity bias secondary to prior radiation treatment to the brain. This is important since neuroimaging studies have documented a link between cranial irradiation and changes in white matter,^{29–32} neurocognitive deficits,^{33–35} and impairments in attention, concentration, memory, and learning.^{36–38} Moreover, by focusing only on advanced stage neuroblastoma, we were better able to ascertain whether there were any specific interactions between treatment and disease entity that could impact neuropsychological development. Lastly, by including a comprehensive neuropsychological battery which focused not only on intellectual functioning but also on other dimensions of neurocognitive and neurobehavioral functioning, we were able to identify a specific neuropsychological profile for this cohort of patients.

The emergence of a neuropsychological profile of specific strengths for this cohort of neuroblastoma survivors has not been previously documented in the literature. A preliminary finding of increased intellectual functioning has been reported for a group of neuroblastoma patients,⁹ however, the ability to compare those findings with our results is limited because the specific stage and treatment regimen were not identified. It is noteworthy that 94% of our cohort exhibited superior performance on at least one task and 69% exhibited superior performance on five or more measures. Although the specific basis for this profile we have observed is unknown, possible hypothetical explanations for this profile include various influences. Biologically, some researchers have suggested that the presence of a neuroblastoma during a period of increased brain development may be associated with biological or chemical changes in the developing brain which may promote better neuropsychological functioning.³⁹ Methodologically, our sample of survivors may have been biased to families who were more motivated or were more psychosocially adaptive and resilient in response to a life-threatening illness and who subsequently chose to participate in this long-term follow-up research study. Furthermore, given that almost half of the parents had received post high-school degrees, the strengths identified in this profile may also reflect the parent's emphasis on providing stimulating learning experiences for the children. In addition, although we do not have more specific employment data for the parents of the children in this cohort, it is possible that this pattern of performance may also have been influenced by SES factors. Lastly, in regards to superior verbal functioning, since these survivors were treated during their preschool years, they perhaps were able to derive language and socialization benefits from their exposure to adult interactions during a significant period in language development. Furthermore, hearing status did not appear to impact verbal development since hearing loss had either been corrected with hearing aids or was in the high-

frequency range and therefore did not impact conversational speech.

There are some limitations of this study. Our sample was limited in size, which impacted our power to detect smaller neurocognitive and neurobehavioral differences between the TBI and no-TBI groups. In addition, our cohort consisted of primarily females, so any discrepancies in functioning that may be associated with gender were undetectable in this study. We were able to locate and test 57% of our eligible survivors, and may have a select group volunteering their children to participate in research who are not representative of the population as a whole. Finally, we do not have baseline testing available, and cannot assess any declines in neuropsychological outcomes in these patients that occurred over time. However, given the current results and the long follow-up time between diagnosis and neuropsychological testing, if there were declines, they would not likely be clinically significant.

In conclusion, high-risk neuroblastoma remains a significant treatment challenge for clinical researchers who are struggling to determine optimal therapies that will result in increased rates of cure. Although more research is needed, this report describes the neuropsychological functioning of a cohort of advanced stage neuroblastoma survivors, treated at young ages, who received aggressive therapies and whose neuropsychological functioning was not deleteriously impacted.

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