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CLINICAL – PATIENT STUDIES

Intelligence and adaptive function in children diagnosed with brain tumour during infancy

Robyn Stargatt · Jeffrey V. Rosenfeld · Vicki Anderson · Timothy Hassall · Wirginia Maixner · David Ashley

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Abstract
Background Late effects of treatment in children diagnosed and treated for brain tumours in infancy is a major concern. Assessment of infants presenting with brain tumours is difficult and there is little information available regarding the development of infants prior to treatment and hence the impact of the tumour itself on developmental outcomes.
Aim To describe the development of children diagnosed with brain tumours in infancy and to document their cognitive and adaptive function at school entry.
Method Infants were psychologically evaluated at the time of diagnosis of a brain tumour and during their fifth or sixth year in preparation for school entry.
Results Children diagnosed with brain tumours in infancy display developmental delays in a number of areas of adaptive function. By the time these children are school age they display further compromise in cognitive and academic skills and adaptive behaviour. Higher levels of deficit at follow-up were associated with tumour location in the supratentorium, younger age at diagnosis and longer time since diagnosis. The effect of radiotherapy could not be determined because of differing degrees of developmental compromise in the treatment groups at baseline.
Conclusion Brain tumours in infancy confer a risk of poor developmental progress at the time of diagnosis. These children display additional compromise of development by the time they reach school age. Research protocols evaluating the impact of treatment in infants diagnosed with brain tumours need to take account of the developmental status of the child at diagnosis.

Keywords Brain tumour · Infants · Neuropsychology · Intelligence · Adaptive function

R. Stargatt · V. Anderson
Department of Psychology, Murdoch Childrens' Research Institute, Royal Children's Hospital, Melbourne, Vic, Australia

J. V. Rosenfeld
Department of Neurosurgery & Surgery, Alfred Hospital & Monash University, Melbourne, Vic, Australia

T. Hassall
Department of Haemotology/Oncology, Royal Children's Hospital, Brisbane, Qld, Australia

W. Maixner
Department of Neurosurgery, Royal Children's Hospital, Melbourne, Vic, Australia

D. Ashley
Children's Cancer Centre, Royal Children's Hospital, Melbourne, Vic, Australia

R. Stargatt (✉)
Department of Psychology, Royal Children's Hospital, Flemington Rd, Parkville 3052 Vic, Australia
e-mail: robyn.stargatt@rch.org.au

Introduction

The survival rate of children suffering from intracranial tumours has increased significantly over recent years [1]. Survivors generally have a range of cognitive problems [2] and poor academic outcomes [3–6].

Causes of morbidity in children suffering from brain tumour include the nature of the tumour, the type of treatment and the presence of complications and associated pathology such as hydrocephalus [7].

Tumour location in the supratentorium is generally considered to confer poorer functional outcomes than location in the posterior fossa [8] due to the role of cortical areas in subserving sensorimotor, language and cognition.

Treatment for brain tumours includes surgery, chemotherapy and radiotherapy. Morbidity following surgery for brain tumours has declined in the microsurgical era [9] and generally neurological recovery post surgery is good. Methotrexate has been a commonly administered and studied chemotherapeutic agent used in the treatment of malignant brain tumours. In a study [10] of 14 infants with malignant brain tumours neuro-developmental evaluations were conducted at the initiation of chemotherapy, and following, prior to radiotherapy. The majority remained stable or declined while receiving chemotherapy. More recent research results in studies of the effect of chemotherapy in children with Acute Lymphatic Leukaemia generally indicate that intrathecal methotrexate has little impact on cognition [11–13]. In recent treatment protocols a variety of other chemotherapeutic agents are used in combination for both malignant and more benign tumours and the impact of these on cognitive development is less comprehensively studied. One retrospective study [14] of infants under the age of 36 months treated with low dose craniospinal irradiation and chemotherapy concluded that both radiotherapy and chemotherapy contributed to morbidity. In a trial [15] of the use of post operative methotrexate and no radiotherapy in children diagnosed with medulloblastoma under the age of 3 years neuropsychological follow-up was conducted in 14 patients at a median of 4.8 years after diagnosis. These authors concluded that the disease itself, surgery and chemotherapy have a negative effect on neuro-cognitive outcome, suggesting that the infant brain may be more susceptible to chemotherapy as well as radiotherapy. However, this study contained no baseline data making the contribution of therapy difficult to isolate.

It has been consistently demonstrated that conventional dose cranial irradiation is associated with adverse neuropsychological sequelae in children [16, 17], The impact of radiotherapy has also been found to increase with longer time since treatment [2, 18] and in children treated at a younger age [5, 19–21]. In studies of adult survivors following irradiation for treatment of brain tumours at less than 4 years, poor quality of life and considerable compromise of school and work performance has been reported [22]. There is some evidence that a proportion of infants presenting with posterior fossa tumours exhibit developmental delay [23] at diagnosis, but few studies obtain baseline assessments of infants at the time of diagnosis. In the study [10] of 14 infants with malignant brain tumours neuro-developmental evaluations less than one quarter of the children displayed normal developmental status at the initiation of chemotherapy, prior to radiation. A prospective study [24] of neuro-developmental outcome in children treated for medulloblastoma under the age of 5 years documented a mean IQ score at baseline in the ‘‘Low Average’ range and an ongoing decline in intelligence following treatment with chemotherapy and planned delayed radiation.

The aim of this study was to determine whether or not infants diagnosed with brain tumours displayed abnormal developmental status at the time of diagnosis and whether or not they displayed a decline in developmental progress over the period from diagnosis until they turned 5 or 6 years old, the years they would normally enter school.

On the basis of the current literature it was predicted that (a) Infants diagnosed with brain tumours in infancy will display delays in adaptive skills at diagnosis, (b) in addition, delays in adaptive skills, neuropsychological skills and academic skills will be evident at follow-up and (c) that follow-up outcome measures will be influenced by various patient and treatment factors including age at and time since diagnosis, treatment type, age at and time since treatment and tumour location.

Method

Participants

Fifty-two children diagnosed with brain tumours under the age of 5 years (between August 1996 and August 2003) were referred for baseline assessment from the departments of neurosurgery and oncology at the Royal Children’s Hospital, Australia. There were 28 (53.8%) males and 24 (46.2%) females. Of the 52 referred at diagnosis, developmental information was obtained on 40. Failure to obtain data on the remaining children was due to difficulties associated with contact during treatment. Appointments were cancelled due to prioritisation of other medical appointments, changes in treatment planning, changes in health status of child and unscheduled readmissions or discharges. All 52 were maintained in the clinical review process and as many as possible were seen for follow-up in order to capture the majority of survivors. Nineteen children died before their fifth birthday, one was diagnosed with autism and not included in follow-up data, seven

children were treated or moved interstate and three had not reached their fifth birthday by the completion of data collection. Twenty-one children were seen in the year they turned five or six. Of the 21 survivors assessed 13 had baseline data recorded.

Of the original 52 children, 34 (65%) children had posterior fossa (PF) tumours, and 18 (35%) had supratentorial (ST) tumours. Treatment protocols varied considerably. Twenty-three (44.2%) received surgery, chemotherapy and radiotherapy. Three (5.8%) received surgery and radiotherapy without chemotherapy. One (1.9%) underwent biopsy only, two (3.8%) biopsy and chemo, six (11.5%) surgery only, three (5.8%) chemo only, 14 (26.9%) surgery and chemo.

Survivors

Twenty-one children were seen at follow-up, 13 with PF tumours and eight with ST tumours. Seven of the PF group had radiotherapy (three according to the SJMB96[1] protocol and four according to the ANZCCSG BabyBrain 99[2] protocol). Four of the ST group had radiotherapy. Mean age at follow-up was 5.54 years (n = 21, SD = 0.41, range = 4.4–6.2). The mean time between baseline and follow-up was 24.62 months (n = 13, SD = 14.26, range = 3.2 months–62.01). Of those who had received radiotherapy the mean age at the completion of treatment was 4.09 years, (SD = 0.62, range = 3.09–4.99). Time in months between completion of radiotherapy and the follow-up assessment was 17.10 months (SD = 7.6, range = 4.20–27.17). Table 1 describes the tumour, treatment and outcome characterises of these survivors.

Measures

The Vineland Adaptive Behaviour Scale (VABS) assesses personal and social sufficiency and provides age related Standard Scores [25]. The VABS is a structured interview conducted with the parent in order to determine the child's level of function in four domains. These are Communication, Daily Living, Socialization and Motor Skills Domains[3]. Each domain is composed of questions regarding skills in each area that are accomplished along a developmental trajectory. The parent is asked both general and specific questions about a general skill area in order to elicit a set of scores based on whether the child usually, sometimes or partially, or never, exhibits a specific skill. The child is not required to participate in any activities directly with the examiner. This interview was conducted as soon as possible following referral. The parent was directed to consider the child's best level of development just prior to diagnosis. This was done to establish the level of ability reached by the child prior to surgery and prior to the possible recent decline or symptoms that precipitated diagnosis. As such this instrument is able to capture the best developmental level reached by the child without that result being contaminated by the child's level of co-operation, illness or post-operative symptoms. This Scale was administered at baseline and was readministered at follow-up along with tests of intellectual function (Wechsler Preschool and Primary Scale of Intelligence-Revised [26]), memory and learning (California Verbal Learning Test [27]) academic Skills (Wechsler Individual Achievement Test [28]), verbal fluency (A Developmental Neuropsychological Assessment-NEPSY [29]) and visuo-motor integration [30]. Table 2 lists the domains assessed, the tests used and their variable labels. All scores are reported as Standard Scores with mean = 100 and SD = 15 apart from the CVTOT reported as a T-Score with mean = 50 and SD = 10, the CVSD and CVLD as z-scores with mean = 0 and SD = 1 and the FLUENT as a Scaled Score with mean = 10 and SD = 3, as per the individual test manuals.

Procedure

All children presenting for investigation and treatment of tumour to the departments of neurosurgery or oncology, under the age of 5 years, were referred for baseline assessments. Baseline assessments were conducted at, or around the time of diagnosis by a Neuropsychologist (RS). Mean age at baseline was 2.67 years (SD = 1.37, range = 0.2–5.0). Follow-up assessments were conducted as part of normal clinical practice when the child reached their fifth or sixth birthday. All testing, approximately 2 h, was conducted over the period of 1 day with the opportunity for breaks as required by the child. Order of test administration was fixed.

Statistics

The Shapiro–Wilk test for normal distribution and the Levene test for equality of variances between variables

[1] St Jude Medulloblastoma 1996

[2] Australia and New Zealand Children's Cancer Study Group Baby Brain 1999

[3] In this age group Communication Skills refer to the child's ability to understand what is said to them and to use language to communicate with others. Daily Living Skills refers to feeding, toileting and dressing. Socializations Skills refer to interaction with others and play. Motor Skills refer to sitting, crawling and walking etc and manual dexterity

Table 1 Tumour, treatment and outcome characteristics of 21 survivors

No.	Sex	Tumour type	PF/ST	Location	Treatment	R dose	Status	Age-B	Age-F	Months B–F	Age F	Months B–F	ABC-B	ABC-F	FSIQ
1	M	Pilo-astro	PF	Brainstem	C			4.9	5.3	3.2			83	82	87
2	M	Pilo-astro	ST	Right temporal	S & C		Recurrence	2.3	4.4	25				72	85
3	F	PNET	ST	Right frontal	S, C & R	55 + 23.4		4.1	5.5	15.6	4.25	14.1	105	94	96
4	F	Epend	PF	Posterior fossa	S & R	54		2.8	5.2	27	3.09	24.5		107	78
5	F	Epend	PF	Posterior fossa	S, C & R	54	Recurrence	4.3	5.1	8	4.68	4.2			98
6	F	Glioma	PF	Pontine	Biopsy			2.8	5.6	32				53	56
7	M	Epend	PF	Posterior fossa	S & R	54	Recurrence	4.6	5.9	13.63	4.73	12.6	96	116	121
8	M	Medull	PF	Posterior fossa	S, C & R	55.8 + 36	Recurrence	3.1	5.6	29.97	3.46	25.13	103	66	64
9	M	PNET	ST	Left frontal/parietal	S, C & R	53.8 + 23.4		4	5.7	19.8	4.99	8.07	94	94	84
10	F	Pilo-astro	PF	Posterior fossa	S			2.9	5.8	34				120	103
11	F	Medull	PF	Posterior fossa	S, C & R	54		3.6	5.1	17.53	3.76	15.23	119	93	102
12	M	Pilo-astro	ST	Optic chiasm	Biopsy & C			4.2	5.7	17.97			78	72	90
13	F	Epend	PF	Posterior fossa	S, C & R	54		3.6	6.2	29.53	4	25.23	92	91	92
14	M	GBM	ST	Right temporal lobe	S & C		Recurrence	0.3	5.4	62.07			94	44	44
15	M	Pilo-astro	PF	Posterior fossa	S			2.3	5.5	36				91	86
16	M	Epend	ST	Right temporal	S & R	50.4	Recurrence	2.5	5.7	9.25	3.35	27.17	100	101	84
17	F	Pilo-astro	ST	R hypothalamus	S & C			2.5	5.1	30				81	74
18	F	Pilo-astro	PF	Posterior fossa	S			5	6.2	13.43			90	94	102
19	F	Epend	ST	Right parietal lobe	S, C & R	51	Recurrence	3.8	5.7	22.17	4.51	13.93	107	90	113
20	F	Medull	PF	Posterior fossa	S, C & R	55.8 + 23.4		4.1	5.8	18.7	4.2	17.97	89	85	78
21	F	Epend	PF	Posterior fossa	S & C		Rept surgery	4.6	5.6	11.2				110	102

M, Male; F, Female; PF, Posterior Fossa; ST, Supratentorial; Pilo-astro, Pilocytic astrocytoma; Epend, Ependymoma; Medull, Medulloblastoma; PNET, Primitive neuroectodermal tumour; GBM, Glioblastoma multiforme; S, Surgery; C, Chemotherapy; R, Radiotherapy; Age-B, Age at baseline in years; Age-F, Age at follow-up (in years, Months B–F = months between baseline and follow-up). Age-R, Age at radiotherapy; Months R–F, Months since radiotherapy; ABC, Vineland adaptive behaviour composite; FSIQ, Full Scale IQ score

Table 2 Developmental and neuropsychological tests administered

Domain	Test name	Variable label*
Communication skills	Communication Domain Vineland Adaptive Behaviour Scale	COM
Daily living skills	Daily Living Domain Vineland Adaptive Behaviour Scale	DLS
Socialization skills	Socialization Domain Vineland Adaptive Behaviour Scale	SOC
Motor skills	Motor Domain Vineland Adaptive Behaviour Scale	MOT
Adaptive skills	Vineland Adaptive Behaviour Composite Score	ABC
Visuo-spatial skills	Performance IQ—WPPSI-R	PIQ
Verbal skills	Verbal IQ—WPPSI-R	VIQ
Intellectual skills	Full scale IQ—WPPSI-R	FSIQ
Learning	California Verbal Learning Test Total Score	CVTOT
Short delay recall	California Verbal Learning Test—Short Delay Score	CVSD
Long delay recall	California Verbal Learning Test—Long Delay Score	CVLD
Reading	Reading Subtest—Wechsler Individual Achievement Test	READ
Mathematics	Mathematics Subtest—Wechsler Individual Achievement Test	MATH
Spelling	Spelling Subtest—Wechsler Individual Achievement Test	SPELL
Verbal fluency	Verbal Fluency Subtest—NEPSY	FLUENT
Visuomotor integration	Beery–Buktenica Developmental Test of Visuo-Motor Integration	VMI

*The suffix—B used in text denotes administration at baseline and—F denotes administration at follow-up. WWPSI-R: Wechsler Pre School and Primary Scale of Intelligence—Revised

were conducted on all variables to be examined. Multiple *t*-tests were used to examine the differences between the participants and normative data on each of the outcome variables at baseline and follow-up. Bias corrected standardized effect sizes are reported [31]. Linear and partial correlations analyses were used to determine associations between participant and outcome variables.

Results

Adaptive skills at diagnosis (n = 40)

Data from the VABS for 40 children was available at baseline. The mean for all Domains (Communication Skills, Daily Living Skills, Socialization Skills and Motor Skills and the Adaptive Behaviour Composite) were all within the ''Average'' range (see Table 3). One sample *t*-tests, however, comparing the group means with normative data indicate that the group means were significantly below the normative means on Daily Living Skills, $t(39) = -3.39$, P=0.002, Socialisation Skills, $t(39) = -2.60$, $P = 0.01$, Motor Skills, $t(39) = -3.57$, $P = 0.002$ and the Adaptive Behaviour Composite, $t(39) = -3.57$, $P = 0.001$.

Independent samples *t*-tests found no significant difference between any of the VABS Scores by gender or tumour location and there was no significant correlation with any of the VABS scores and age at diagnosis.

Table 3 VABS at baseline (n = 40)

	M	SD
COM-B	97.35	14.20
DLS-B*	92.95	13.17
SOC-B*	94.28	13.93
MOT-B*	93.80	11.94
ABC-B**	92.68	12.99

*$P < 0.01$, **$P < 0.001$

Adaptive skills at follow-up (n = 21)

Twenty-one children were administered the VABC at follow-up. The mean for all domains and the Adaptive Behaviour Composite were within the ''Low Average''–''Average'' range (see Table 4). One sample *t*-tests comparing the group means with the normative data indicate that the group means were statistically significantly below the normative means on Communication Skills, $t(20) = -3.11$, $P = 0.006$, Daily Living Skills $t(20) = -2.65$, $P = 0.016$, Motor Skills, $t(20) = -2.830$, $P = 0.010$ and the Adaptive Behaviour Composite, $t(20) = -2.83$, $P = 0.010$.

Neuropsychological and academic skills at follow-up (n=21)

Table 5 presents results from the neuropsychological and academic tests. As can be seen by the range of scores there is considerable variation in the group as a whole. For example, intellectual ability ranges from more than three standard deviations below the mean to more than one standard deviation above the mean. Similar extremes are found in all scores. Visual analysis

Table 4 VABS at follow-up ($n = 21$)

	M	SD
COM-F*	87.24	18.80
DLS-F$^+$	90.67	16.17
SOC-F	96.57	17.34
MOT-F*	86.71	21.51
ABC-F*	88.24	19.08

$^+P < 0.05$, $*P < 0.01$

finds that apart from FLUENT all means are below the means in the normative data.

Statistically significant differences between the participants' mean scores and the normative data were found on tests of general intellectual abilities including visuo-spatial skills (PIQ), $t(20) = 2.34$, $P = 0.03$, verbal skills (VIQ), $t(20) = -3.50$, $P = 0.002$, and general intelligence (FSIQ), $t(20) = 3.227$, $P = 0.004$, memory following a long delay (CVLD), $t(14) = 2.56$, $P = 0.023$, spelling (SPELL), $t(20) = -3.37$, $P = 0.003$, and visuo-motor integration (VMI), $t(18) = -4.22$, $P = 0.001$.

Age at diagnosis and time since diagnosis

Pearson correlations with one tailed test of significance were used to determine the strength of the association between age at diagnosis and the time since diagnosis on the follow-up test results in those areas that differed significantly from normative data (FSIQ, CVLD, SPELL, VMI and ABC-F).

Significant correlations were found between age at diagnosis and intellectual ability, FSIQ ($r = 0.66$, $P = 0.014$) and adaptive behaviour at follow-up, ABC-F ($r = 0.52$, $P = 0.05$) indicating older age at diagnosis was associated with better outcome. Significant correlations were found between time since diagnosis and intellectual ability, FSIQ ($r = -0.57$, $P = 0.034$) and adaptive behaviour, ABC-F ($r = -0.570$, $P = 0.034$) indicating that the longer the time since treatment the worse the outcome. There was a significant correlation between age at diagnosis and time since diagnosis($r = -0.80$, $P = 0.001$) indicating these two variables are confounded. No significant correlations were found between age and time since diagnosis on the other variables.

Table 5 Neuropsychological and academic results at follow-up ($n = 21$)

	M	SD	Range
PIQ$^+$	90.67	18.27	51–126
VIQ*	87.24	16.69	50–112
FSIQ*	88.10	17.68	44–121
CVTOT	44.73	10.40	28–69
CVSD	–0.300	0.88	–2.0–1.5
CVLD$^+$	–0.667	1.01	–2.5–0.5
READ	95.71	14.56	50–127
MATH	94.33	14.19	50–121
SPELL*	87.86	16.51	50–119
FLUENT	10.89	3.43	3–19
VMI**	88.16	12.24	67–109

$^+P < 0.05$, $*P < 0.01$, $**P < 0.001$

Tumour location

Intellectual ability and adaptive behaviour in survivors in both the PF and ST groups is presented in Table 6. Visual analysis suggests slightly worse outcomes for the ST group but there were no statistically significant differences between FSIQ scores in PF vs. ST groups, $t(19) = 0.740$, $P = 0.489$, or ABC-F, $t(18) = -1.37$, $P = 0.208$. A moderate Effect Size was find between the groups on the ABC-F (ES = 0.06).

Treatment type

There was considerable variability in the treatments received. The survivor group was divided according to those who had radiotherapy included in treatment and those who had not. Nine had surgery, chemotherapy and radiotherapy and three had surgery and radiotherapy, the remaining nine had combinations of biopsy, surgery and chemotherapy but not radiotherapy. Summary results are presented in Table 7.

Initial analysis on the adaptive skills data at baseline was conducted to determine if there were differences between the survivors who were ultimately treated with radiotherapy or not. The mean ABC-B differed by almost one standard deviation between the two groups. This difference reaches statistical significance ($t = -2.74$, df = 11, $P = 0.019$). Against expectations the group who received radiotherapy scored more

Table 6 Tumour location, intelligence and adaptive behaviour

	PF ($n = 13$) M (SD)	ST ($n = 8$) M (SD)
FSIQ	89.90(17.74)	83.75(19.72)
ABC-F	92.42(19.64)	81.00(18.32)

Table 7 Treatment groups, intelligence and adaptive behaviour

Treatment	Baseline ABC-B	Follow-up ABC-F	FSIQ
No radiotherapy	86.24 (7.14)	78.79 (22.55)	80.74 (19.75)
Radiotherapy	100.56 (9.21)	95.18 (13.54)	92.67 (16.05)

highly on FSIQ and ABC-F than those who did not receive radiotherapy. None of these differences at follow-up reached statistical significance. It is of some considerable interest however that *before* treatment the children who went on to receive radiation scored more poorly on the VABC-B than the children who went on to receive treatment that did not include radiotherapy. This data demonstrates the importance of obtaining baseline data and the considerable difficulty that exists in making assumptions about equality of tumour and treatment groups on developmental variables. The results displaying a difference between the two groups at baseline suggest that effect of treatment cannot be separated from effect of the initial differences in development.

Age and time since treatment for children treated with radiotherapy

Eleven of the 21 survivors were treated with radiotherapy. The mean age at which the radiotherapy treatment was completed was 4.09 years and the mean time since completion of the radiotherapy was 17 months. No significant correlations were found between age at radiotherapy or time since radiotherapy on the outcome measures.

Posterior fossa tumours with and without radiotherapy

Seven children with PF tumours received radiotherapy and six did not. Only seven of these children had undergone baseline assessment. The mean ABC-B of the two children who had no radiotherapy was 86.50 (SD = 4.95). This suggests that these two children had mild delays in development. While this is informative it is not reasonable to suggest that results based on these two children can be extrapolated to be representative of the greater population of children who present with PF tumours. This data may also indicate a relationship between presentation with developmental delay and treatment decisions. The mean VABC-B of the five children who had baseline assessments and went on to have radiotherapy was 99.80 (SD = 11.95). This figure suggests the group who did go on to have radiotherapy had normal development at the time of diagnosis. The mean VABC-F score in this group was 93.00 (SD = 17.45). While it is possible that the 6 point difference in the two scores represents a decline this cannot be demonstrated statistically in such a small group and the difference does not reach a moderate effect size (ES = 0.45).

Table 8 VABS at baseline and follow-up (n = 13)

	Baseline M (SD)	Follow-up M (SD)
COM*	100.00 (10.82)	84.92 (16.36)
DLS	97.62 (7.75)	90.15 (17.13)
SOC	98.31 (13.46)	95.69 (19.24)
MOT	93.77 (11.70)	84.85 (19.28)
ABC	96.15 (10.79)	86.38 (17.74)

*$P < 0.01$

Adaptive function at baseline and follow-up (n=13)

Only 13 children were assessed at both the baseline and the follow-up on the VABS due to difficulties in data collection. The results are presented in Table 8.

A visual analysis reveals deterioration in all domains to a greater or lesser extent across time. Paired sample t-tests indicates that this difference reaches statistical significance in the Communication Domain, $t(12) = 3.094$, $P = 0.009$. The 10 point difference between the ABC scores approaches, but does not reach statistical significance, $t(12) = 1.886$, $P = 0.084$. Effect size analyses finds this to be a moderate effect size ABC (ES = 0.64). Effect size analysed also finds a clinically significant effect size in the difference between baseline and follow-up on COM (ES = 1.05) and moderate effect sizes on DLS (ES = 0.54) and MOT (ES = 0.54).

Discussion

Infants diagnosed with brain tumours in infancy display variable developmental progress in adaptive behaviour. Some infants display delays in adaptive behaviour at diagnosis. As a group, children diagnosed with brain tumours in infancy display delays in daily living skills, socialisation skills, motor skills and general adaptive behaviour skills compared with normative data. This is consistent with a previous report [24] of the variability in IQ scores in children assessed at baseline. These authors reported a median baseline IQ value of 88, and a range of 50–111. This analysis indicates it is critical to have baseline information in order to meaningfully evaluate follow-up data. It also raises the question that treatment decisions may be made on the basis of the developmental status of the child at presentation.

Children who survive diagnosis and treatment of tumour in infancy display deficits of skills in communication, daily living, motor skills and general adaptive behaviour in the year of their fifth or sixth birthday. These children also display deficits of visuo-spatial skills, language skills, general intellectual ability,

memory, visuo-motor integration and spelling. Follow-up assessments were conducted in the year in which children generally begin formal schooling. The deficits in adaptive behaviour and cognitive skills have considerable implications for school placement, support requirements and social and academic achievement.

Outcomes in adaptive behaviour and neuropsychological function were associated with age at diagnosis and time since diagnosis. Poorer outcomes were associated with both younger age of diagnosis and longer time since diagnosis, although these two variables were also confounded. Interestingly at the time of diagnosis there was no correlation between age and adaptive behaviour. This suggests that a significant arrest of development occurs at or around the time symptoms precipitate diagnosis and treatment. The average time since diagnosis was approximately 2 years. The drop in the Standard Scores on the Communication Skills Domain of the VABS was 15 points and the ABC was 10 points. A prospective study [24] of neuro-developmental outcome in children treated for medulloblastoma under the age of 5 years with chemotherapy and planned delayed radiation documented a decline in intelligence at the rate of 3.9 points per year. The drop in points on the VABS and Communication Skills Domain was greater than this in this study.

There was no difference between survivors who received radiotherapy (in both the PF and ST groups) and those who did not on the outcome measures. However, the treatment groups were dissimilar in terms of their development at baseline and time since treatment was short with the average time since completion of radiotherapy just 17 months. Previous studies have shown that the effect of radiotherapy increases with time since treatment. Children with PF tumours who received radiotherapy did appear to show a decline in adaptive behaviour but subject numbers were too small for meaningful statistical analyses. The 6 point drop in the ABC scores over time is however approximately consistent with the drop in skills found in Walter et al. [24] study.

Clearly, delays in developmental status at the time of diagnosis indicate that the tumour has an effect on the developing brain of infants. Moderate and clinically significant effect sizes indicates decline in adaptive skills over time and statistically significant deficits compared with normative data in children at follow-up approximately 2 years later. The effect of individual treatments could not be isolated in this study firstly as the children who received radiotherapy and those who did not were not equivalent in terms of their development prior to treatment and secondly due to small subject numbers. In addition, radiotherapy is used in the treatment of the most aggressive tumours. Theoretically it is not possible to determine whether psychological deficits that occur during the treatment period are due to the impact of the growing tumour or to the impact of the treatment. However other studies [14, 15] have concluded that chemotherapy does have an impact on the psychological skills and the majority of the impact of radiotherapy has been found to occur following treatment completion in other studies.

One of the most important findings demonstrated by this study is the importance of baseline testing for children at the time of diagnosis of a brain tumor. It should be a standard of care for children with brain tumours. This study also demonstrates that these children are at high risk of academic failure. Further research needs to be conducted in order to determine the ongoing nature of difficulties experienced by these children.

This study has a number of limitations. Several initial baseline assessments could not be conducted due the difficulty of making contact and appointments with parents of children at the time of diagnosis. This is probably due initially to the mobility of parents at this stage and the fact that parents stay in hospital wards or alternative accommodation while their child is hospitalised and are not easily located. Appointments made were also often cancelled as the status of the child deteriorated and they were readmitted to hospital. The demands of care of other children in young families occasionally took precedence over appointments. A number of referrals were also made for baseline assessments of children who ultimately received treatment at other institutions. There was also a very high attrition due to death. This resulted in small subject numbers and the associated lack of power in the statistical analyses. Furthermore, additional data collection during the years between baseline and school entry would have allowed a repeated measures analysis that would have increased the power of the study. Comparison with a control group of children treated for non-neurological tumours may be helpful in better understanding the contribution of the tumour and its treatment to adaptive function and intellectual ability.

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