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Cognitive Function in Children With Brain Tumors in the First Year After Diagnosis Compared to Healthy Matched Controls

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Background. Improved survival of children with brain tumors (BTs) has increased focus on ameliorating morbidity. To reduce the risk of progressive cognitive decline, remedial strategies need to be instituted early, based upon accurate appraisal of need, yet few studies have investigated cognition in BT children early post-diagnosis. The study aims were to investigate cognition in children with primary BTs 1, 6, and 12 months post-diagnosis compared with healthy children, exploring the impact of disease and treatment variables. ***Methods.*** Forty-eight children aged 2–16 years with primary BTs, referred to a Regional Neurosurgical Unit over the 2-year study period were eligible for enrolment. The "best friends" model was used to recruit matched controls. Cognition was assessed using age-appropriate Wechsler Intelligence scales; Children's Memory Scale; Test of Everyday Attention for Children, and Wechsler Quicktest. ***Results.*** Patients with BTs had significantly reduced performance compared to controls early post-diagnosis in tests of Performance IQ, processing speed, verbal and visual memory, and selective attention. Improved performance over 12 months was seen in patients with BTs although also, for some measures, in controls. Significant deficits in cognitive performance were seen one year post-diagnosis for Verbal IQ; processing speed, visual and verbal immediate memory, and selective attention. Infratentorial site, high tumor grade, hydrocephalus, radiotherapy, and chemotherapy were associated with poorer functioning. ***Conclusion.*** Early cognitive impairment is present in BT children, sometimes prior to radiotherapy/chemotherapy treatment, and is associated with hydrocephalus, high tumor grade and infratentorial site. Future studies should investigate the role of early rehabilitation in improving cognition. Pediatr Blood Cancer 2014;61:464–472. © 2013 Wiley Periodicals, Inc.

Key words: brain tumor; chemotherapy; child; cognition; outcome; radiotherapy

INTRODUCTION

Brain tumors (BT) are the second most common form of pediatric cancer [1]. Prognosis has significantly improved, approximately 65% of BT children now achieving long-term survival [2]. As a consequence, there is increased focus on preventing or ameliorating morbidity in survivors [3].

Long-term follow-up studies of BT children have demonstrated a range of cognitive deficits, involving verbal and performance IQ; short and long-term memory; attentional abilities; executive function; and academic performance [4–6]. Research has highlighted the negative impact of cognitive sequelae upon quality of life (QoL) [7,8]. Important variables affecting cognition include tumor type and location; complications such as hydrocephalus; treatment, including surgery, cranial irradiation treatment (CRT) and chemotherapy; and age [3–5,9]. Most pediatric patients with BTs will experience several factors. In the context of long-term follow-up studies, this makes it difficult to disentangle the effects of different variables [9].

To help reduce the risk of progressive cognitive decline, remedial strategies need to be instituted early, based upon accurate appraisal of need [10,11]. Most previous research has involved retrospective long-term follow-up studies. Cognition in patients with BTs has generally been compared with population normative data, rather than matched controls, which may underestimate acquired deficits. Relatively few data exist concerning the evolution of cognitive outcomes, particularly during the first year post-diagnosis.

A study suggested most cognitive indices in BT children to remain stable over repeat testing, the exception being attention, which declined [8]. In contrast, an earlier study [10] demonstrated a progressive decline in IQ over 2–5 years post-diagnosis. A prospective study [11], comparing cognition in children with malignant BTs treated with CRT with those with BTs in similar sites not receiving CRT, demonstrated declines in verbal and performance IQ in the CRT compared to non-CRT group.

The study aims were: (1) to prospectively investigate cognition in children newly diagnosed with a primary BT 1, 6, and 12 months after diagnosis; (2) to compare the results with those obtained in matched healthy children; (3) to investigate the impact of disease and treatment variables.

PATIENTS AND METHODS

Participants

The study forms part of a larger investigation of outcome following BT diagnosis [7,12–14]. All children and adolescents with primary BTs, referred to the South West Regional Neurosurgical Unit at Frenchay Hospital, Bristol, from April 2003 to April 2005 were eligible for enrolment. Cognitive testing was performed in children aged 2–16 years at enrolment. The "best

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friends" model was used to recruit controls matched for age, sex, socio-economic status and, as far as possible, academic attainment [12,15]. Ethical approval was gained from Central and South Bristol Research Ethics Committee.

Cognitive testing was performed approximately 1 (T1), 6 (T6), and 12 (T12) months post-diagnosis. Participants with BTs included in the analysis are all who were alive at 12 months [12]. To reduce loss of data, all controls recruited were included in the analysis, even if their index participant had died.

Cognitive Measures

Intellect. Age-appropriate Wechsler Intelligence scales measured Performance and Verbal IQ (PIQ and VIQ) and speed of information processing. The Wechsler Intelligence Scale for Children—Third Edition (WISC-III^{UK}) [16] was used in participants aged 6–16 years and Wechsler Preschool and Primary Scale of Intelligence—Revised (WPPSI-R) [17] in children aged 3–5 years. A few participants aged >16 years at the time of later assessments were tested using the Wechsler Abbreviated Scale of Intelligence (WASI) [18].

Memory. Memory function was assessed in children aged 5–16 years by Children's Memory Scale (CMS) [19], providing measures of visual and verbal learning, recall and recognition and a global measure of memory function (General Memory Index, GMI). The Wechsler Memory Scale was used for participants aged >16 years [20].

Attention. Attention was assessed by Test of Everyday Attention for Children (TEA-Ch) [21]. Four subscales are reported; Map Mission and Sky Search (selective attention), Score! (Sustained attention), and Sky Search Dual Task (divided attention).

Academic ability. Academic ability was assessed by Wechsler Quicktest [22], providing measures of reading, spelling, mathematical reasoning abilities. The composite score gives an overall impression of academic performance.

Disease and Treatment Variables

Illness-related variables included site (supra vs. infratentorial) and tumor grade (high vs. low) by revised WHO classification system [23]; presence or absence of hydrocephalus at diagnosis, confirmed on neuroimaging; and use of CRT and/or chemotherapy. Previous research suggests higher tumor grade, presence of hydrocephalus, and exposure to CRT and/or chemotherapy may be associated with poorer outcomes [24–31].

Statistical Analysis

The primary independent variable was tumor group, patients with BTs representing the experimental group, and "best friends" the control group. The secondary independent variable was time since diagnosis (T1, T6, T12). A mixed design was used to compare performance of the groups (between-groups variable) across the three time intervals (within-groups variable), for measures of VIQ and PIQ, processing speed, verbal and visual memory, and academic ability (dependent variables). Results were analyzed using mixed ANOVA using SAS using the "Proc MIXED" procedure in SAS version 9.1 (SAS Inst. Inc., 2002–2003, Cary, NC) which allowed for missing measurements presumed "missing at random." A compound symmetry model was used throughout but allowing the variance–covariance matrix to differ between patients with BTs and controls for Verbal/Visual Immediate/Delayed memory. The two groups were compared at each time point, a priori, irrespective of whether or not the group-by-time interaction was significant. Group by time interactions are only reported if statistically significant. All available data were included in the analysis, conditional on the child's survival to 12 months.

Further independent patient variables, namely, lesion site (supratentorial/infratentorial); tumor grade (high/low); hydrocephalus (presence/absence); treatment (radiotherapy, chemotherapy); age and sex were explored in separate analyses.

RESULTS

Participants

Forty-eight patients with BTs were eligible for the main study. Three declined to participate, 45 were enrolled. Thirty-nine were aged 3–16 years (or reached the age of 3 within a year following diagnosis) at recruitment and eligible for the cognitive study. Five (12.8%) died before T12 assessment, leaving 34 patients with BTs to be included the cognitive analysis. One child, aged 2.3 years at enrolment, was unable to complete cognitive testing. In total, results are reported for 31 BT children; two withdrew from the study following T1 assessment.

Table I provides patient details. For patients with BTs at T1, median age was 9.3 years (range 2.7–16.6); 16 were females, 15 males. Mean time from definitive diagnosis to T1 assessment was 1.8 months (range 0.9–3.7), and to T12 assessment 14 months (range 12–18.7).

Complexity of post-operative management was the main cause of delay in completing T1 assessments. Fifteen patients with BTs had supratentorial tumors, 16 infratentorial. Eight had hydrocephalus at presentation. Thirteen had a high grade tumor and 18 had a low grade tumor. Eighteen had CRT; seven had chemotherapy. Twenty-two (70%) had neurological sequelae, including two patients that were affected by post-fossa syndrome with associated cerebellar mutism.

Median time between diagnosis and radiotherapy commencement was 2.8 months (range 1.8–9.3 months); 16 children had radiotherapy following T1 assessment. Median time between diagnosis and chemotherapy commencement was 6 weeks, range 22 days to >12 months; 5 had chemotherapy before T1 assessment. Controls were recruited for all but two patients with BTs. Thirty-seven controls were thus enrolled into the cognitive study. Controls were retained in the analysis if a patient died or withdrew from the study, to avoid data loss. For controls at T1, median age was 9.9 years (range 2.82–17.8); 19 were females, 18 males.

Cognitive Results

Verbal IQ. Patients with BTs performed significantly worse than controls overall (main effect $P = 0.025$). Although the group by interaction was not significant, the group mean difference increased with time (Table II and Fig. 1). Changes with time were not significant in either group ($P = 0.68$ and 0.10 for patients with BTs and controls, respectively).

Performance IQ. There were significant differences between patients with BTs and controls overall ($P = 0.011$). While the interaction failed to reach significance ($P = 0.10$), group differences decreased with time (Table II and Fig. 1). PIQ scores improved in both patients and controls ($P < 0.001$ and $=0.018$, respectively).

TABLE I. Demographic, Disease, and Treatment Characteristics of Patients With Brain Tumor

Study number	Age T1	Age T6	Age T12	Diagnosis	Sex	Tumor site	Hydro	Grade	Neurological sequelae if present	Radiotherapy	Radiotherapy commenced	Chemotherapy
1	2.7	3.3	3.7	LGA	M	2	1	2	Left hemiplegia, seventh cranial nerve palsy, ataxia bilateral convergent squint	Yes	14 days after T1	Yes
2	3.9	4.5	4.9	LGA	F	2	2	2	Right hemiplegia, ataxia, tremor			No
5	3.9	4.3	5.1	LGA	F	2	1	2	Mild ataxia, left squint, left arm tremor	Yes	137days after T1	Yes
6	4.2	4.7	5.1	LGA	M	1	1	2				No
8	6.0	6.4	6.9	LGA	M	1	2	2				No
10	6.4	6.7	7.4	HGA	F	1	2	1	Left visual field defect, left lower quadrantinopia			No
12	6.4	7.2	7.7	Ependymoma	F	2	1	1	Mild right hemiplegia, right intention tremor, mild ataxia	Yes	1 day before T1	No
13	7.7	8.3	8.7	PNET	F	2	1	1	Left 6th cn palsy, ataxia, loss hearing, speech problem	Yes	14 days after T1	Yes
14	7.7	8.2	8.8	LGA	F	2	1	2	Left hemiplegia, seventh cranial nerve palsy, ataxia, deaf left ear	Yes		Yes
15	7.8	8.4	8.8	LGA	M	2	1	2	Left homonyoushemianopis, left afferent pupil defect, weakness, ataxia, poor co-ordination	Yes	22 days after T1	No
16	8.9	9.3	9.9	LGA	F	2	1	2	Left hemiplegia, posterior fossa syndrome, ataxia, left intention tremor, nystagmus			No
17	9.3	9.9	10.4	LGA	F	1	1	2	No vision in right eye, loss of temporo-inferior vision			No
19	9.3	9.9	10.3	Ependymoma	M	1	2	1		Yes	7 days before T1	Yes
21	9.4	10.0	10.4	PNET	F	2	1	1		Yes	21 days after T1	No
25	9.7	10.2	10.7	Craniopharyngioma	F	1	2	2	Bitemporal hemianopia, decreased visual acuity, panhypotituitarism		22 days after T1	No
27	11.3	11.9	12.4	PNET	M	2	1	1	Left hemiplegia, ataxia, left seventh cranial nerve plasy, tremor, double vision, bilateral loss	Yes	112 days after T1	Yes
28	11.7	12.2	12.7	LGA	F	2	1	2	Visual loss left eye			No
30	12.0	12.3	12.9	Craniopharyngioma	M	1	1	2	Blurred vision	Yes	66 days after T1	No
31	12.2	12.7	13.1	GCT	M	1	1	1	Parinauds syndrome[a]	Yes	22 days after T1	No
32	12.5	13.0	13.5	GCT	M	1	1	1	Parinauds syndrome[a]	Yes	55 days after T1	No
33	12.8	13.4	13.9	LGA	F	1	1	2				Yes
35	13.7	14.2	14.6	PNET	M	1	1	1	Diplopia, parinauds syndrome[a], ataxia, diplopia, nystagmus	Yes	244 days after T1	No
36	13.9	14.4	14.9	LGA	M	1	2	2		Yes	64 days after T1	No
37	14.2	14.9	15.3	Meningioma	F	1	2	2	Left inferior quadrantinopia			No
38	14.5	n/a	n/a	PNET	F	2	1	1		Yes	28 days after T1	Yes
39	15.0	15.6	16.3	HGA	M	1	1	1	Post-fossa syndrome			No
40	15.3	15.8	16.3	LGA	M	2	1	2	Diplopia, left hemiplegia, nystagmus, ataxia, tremor	Yes	26 days after T1	No
41	16.0	16.4	17.0	LGA	F	2	1	2	Right hemiplegia, right facial nerve palsy, tracheostomy, gastrostomy, generalized weakness, ataxia			No
42	16.5	16.7	17.3	GCT	M	1	2	2				No
44	16.6	n/a	n/a	PNET	M	2	1	1	Ataxia, diplopia, post-fossa syndrome	Yes	42 days after T1	Yes
45	16.6	17.1	17.6	HGA	M	2	1	1	Right hemiplegia, ataxia	Yes	221 days after T1	No

Diagnosis: LGA, low grade astrocytoma; HGA, high grade astrocytoma; PNET, primitive lneuroectodermal tumor; GCT, germ cell tumor. *Tumor site*: 1, supratentorial; 2, infratentorial. *Hydrocephanlus*: 1, no hydrocephalus; 2, hydrocephalus. *Tumor grade*: 1, high grade tumor; 2, low grade tumor. [a]Parinaud's syndrome is a cluster of abnormalities of eye movements and pupillary function caused by lesions in the upper brain stem.

TABLE II. Cognitive Results Obtained in Patients and Controls at T1, T6, and T12

	T1							T6							T12						
	Patients			Controls				Patients			Controls				Patients			Controls			
	Mean	SD	N	Mean	SD	N	*P*	Mean	SD	N	Mean	SD	N	*P*	Mean	SD	N	Mean	SD	N	*P*
PIQ	91.7	18.3	31	104.6	16.6	35	0.001	101.9	17.2	30	112.2	13.9	32	0.060	104.2	17.5	30	113.3	13.9	31	0.096
VIQ	96.4	16.2	31	102.1	17.2	36	0.088	97.8	15.2	30	107.1	14.2	32	0.041	96.9	14.6	30	108.2	14.9	31	0.015
PS	83.8	20.8	24	102	21.4	27	0.002	90.1	22	24	110.5	13.4	23	0.002	96.4	24.6	22	111.8	17.6	22	0.005
Vis imm	88.4	21.8	25	104.6	15	30	0.001	103.1	18.7	24	114.7	16.3	20	0.041	102.6	24.5	25	120.3	12.9	23	0.003
Vis del	87.5	25.5	25	102.2	15.1	30	0.003	106	13.4	24	108.7	16.4	20	0.860	109.2	22	25	118.4	13.9	23	0.200
Ver imm	82.6	28.8	23	101.9	19	31	<0.001	96	17.1	23	108.7	21	19	0.057	98.8	20.8	24	116.2	16.7	23	0.018
Ver del	87.6	25.1	23	104.3	19	31	0.002	96.4	17.7	23	108.3	20	19	0.120	100.4	19.7	24	113.8	15	23	0.160
General memory	87.5	22.7	23	105.8	20.3	29	<0.001	100.3	20	22	114.7	22.7	18	0.058	104.3	25.2	24	124.1	15.2	22	0.021
Sky search	7.6	3.6	21	8.6	3.3	26	0.140	9.1	3.7	20	10.7	3	21	0.039	9.8	3.3	22	10.7	2.1	21	0.260
Score!	8.4	3.6	20	9.3	4	27	0.280	8.7	3.2	20	10.8	3	21	0.069	10.6	2.7	21	11	3	22	0.730
Sky search dt	5.7	3.7	19	7.1	3.3	25	0.096	6	2.9	20	7	2.9	21	0.190	7	4	21	8.2	1.8	21	0.210
Map mission	3.5	2.6	20	5.5	2.5	25	0.004	4.3	2.6	20	6.9	2.4	20	0.002	4	2.7	22	6.1	2.5	21	0.013
Reading	94	14	19	102	18.9	24	0.130	100.7	15.5	18	101.2	24.3	20	0.950	93.1	15.9	21	106.6	11.3	20	0.037
Maths	103	15.5	19	111.3	21.2	24	0.220	110.3	20.6	18	116.4	19.2	20	0.250	106.3	17.8	21	115.9	15.7	20	0.290
Spelling	92.3	12	18	105.9	15.9	23	0.063	97.3	15.2	18	107.9	18.1	20	0.018	95.2	16.4	21	107.2	12.2	20	0.039
Composite	94.4	14	18	106.9	22.2	24	0.083	100.2	21.9	18	110.6	19.4	20	0.058	97.4	17.8	21	108.7	13.4	20	0.180

PS, processing speed; vis imm, visual immediate memory; vis del, visual delayed memory; ver imm, verbal immediate memory; ver del, verbal delayed memory composite, academic composite score.

Processing Speed. There were significant differences between patients with BTs and controls overall ($P = 0.001$) with patients with BTs scoring lower than controls at each assessment (Table II and Fig. 1). Both BT and control participants' processing speeds improved with time (both, $P < 0.001$).

Memory. *Visual memory:* For visual immediate memory tasks, patients with BTs scored significantly lower than controls overall ($P < 0.001$) and at each time point (Table II). Scores in both patients with BTs and controls increased significantly over time ($P = 0.004$ and <0.001 respectively).

For the visual delayed memory subscale, the group by time interaction was significant ($P = 0.038$), Both patients with BTs and controls improved over the study period (both, $P < 0.001$) although the improvement in patients with BTs was stalled. Patients with BTs scored significantly lower than controls at T1, but not T6 or T12 (Table II).

Verbal memory: For the verbal immediate subscale, patients with BTs scored lower than controls overall ($P = 0.003$). Both groups increased with time ($P = 0.003$, <0.001).

For the verbal delayed subscale, although the group by time interaction was not significant, the group difference was more marked at T1 (Table II). Scores in patients with BTs increased significantly over time ($P = 0.009$), but the change was not significant in the controls ($P = 0.21$).

General memory index (GMI): The GMI is a composite of verbal and visual memory subscales in immediate and delayed conditions. Patients with BTs had significantly lower scores than controls overall ($P = 0.006$) although the difference failed to achieve significance at T6 (Table II). Scores in patients and controls improved significantly over time (both, $P < 0.001$).

Attention. *Selective attention:* Significant differences between patients with BTs and controls were seen on measures of selective attention. For Map Mission, group differences were significant overall ($P < 0.001$) and at T1, T6, and T12 (Table II). Scores in neither group changed significantly over time ($P = 0.45$, 0.16). For Sky Search, the group difference was just significant ($P = 0.049$). Although the interaction was not significant, the group differences only reached significance at T6 (Table II). There was a significant improvement over time in patients with BTs ($P = 0.007$) and controls ($P = 0.004$).

Sustained attention: There were no significant differences overall between patients with BTs and controls on a measure of sustained attention (Score!) ($P = 0.27$), nor at any time. Although the interaction was not significant, scores improved significantly over time in patients with BTs ($P = 0.006$) but not controls ($P = 0.25$).

Divided attention: There were no significant differences between patients with BTs and controls on a measure of divided attention (Sky Search DT) ($P = 0.056$), Table II. The changes with time were not significant ($P = 0.18$, 0.29).

Academic performance. On the Wechsler Quicktest Reading subscale, the group by time interaction was of border-line significance ($P = 0.0.51$), and patients with BTs scored significantly lower than controls at T12 (Table II). Patients with BTs scored significantly lower than controls overall on the Spelling test ($P = 0.023$). No significant differences between patients with BTs and controls were seen for the Maths subscale (overall $P = 0.20$). Differences between patients and controls on the academic composite score just failed to reach statistical significance (effect of group = 0.064). There were no significant changes with time for any academic subscale.

Impact of disease and treatment variables

Tumor site. Patients with BTs with infratentorial tumors performed more poorly compared to patients with supratentorial tumors in measures of performance IQ at T1 ($P = 0.035$). Although the main effect of tumor site failed to reach statistical significance ($P = 0.063$). There was no significant effect of tumor site in VIQ, processing speed, visual or verbal memory, attention, or academic ability (Table III).

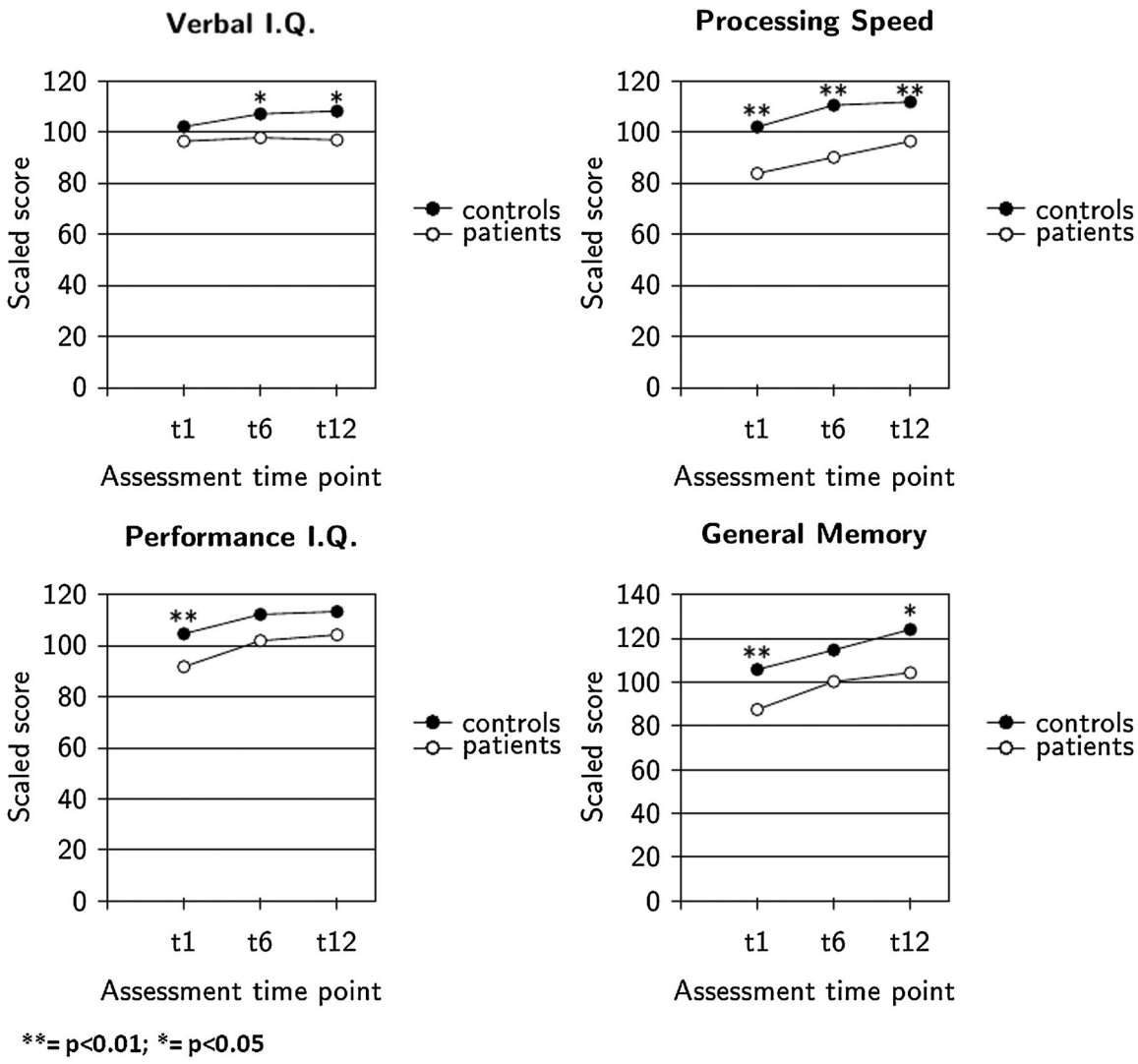

Fig. 1. Verbal IQ (VIQ), performance IQ (PIQ), processing speed index, and general memory index at T1, T6, and T12.

Hydrocephalus. There were significant main effects of hydrocephalus on measure of PIQ ($P = 0.045$), processing speed ($P = 0.011$), and sustained attention (Score!) ($P = 0.029$). In other measures, significant effects were seen at specific time points. Patients with BTs with hydrocephalus had significantly lower GMI scores than those without hydrocephalus at T1, but not at T6 or T12. Additionally, patients with hydrocephalus showed significantly lower scores on a measure of selective attention (Sky Search) at T12. Presence or absence of hydrocephalus had no significant impact on other aspects of attention, or upon VIQ and academic ability (Table III).

Tumor grade. There were significant differences between patients with BTs in terms of tumor grade at various time points. Although the effect of tumor grade on processing speed was not significant overall (main effect $P = 0.084$), patients with high grade tumors had lower processing speed at T12 than those with low grade tumors ($P = 0.020$). Patients with high grade tumors showed reduced performance in the spelling subscale ($P = 0.043$) and composite score of the quicktest at T6 ($P = 0.014$) than those with low grade tumors. There was no significant impact of tumor grade on VIQ, PIQ, memory, attention, or academic ability (Table III).

Radiotherapy. There were no main effects of CRT observed for measures of verbal IQ, performance IQ, or processing speed, though CRT was associated with reduced processing speed at T12 in patients with BTs. A main effect of CRT on general memory in BT patients was identified ($P = 0.018$), though there were no significant main effects of CRT noted on visual or verbal subscales in immediate or delayed conditions. However, patients with BTs who received CRT had significantly lower visual immediate memory and verbal delayed memory scores at T6 and T12 than those who did not. There was a significant main effect of CRT on a measure of divided attention (Sky Search DT; $P = 0.036$). On a measure of selective attention (Sky Search) group differences at T6 and T12 approached statistical significance $P = 0.066$ and 0.054, respectively. There was significant difference at T12 for the Wechsler Quicktest Spelling subscale between those who did and did not receive CRT. There were no significant differences between patients with BTs who did or did not receive CRT with respect to VIQ, PIQ, or other academic abilities (Table IV).

TABLE III. Cognitive Results in Relation to Tumor Variables

	T1							T6							T12						
	Infratentorial			Supratentorial				Infratentorial			Supratentorial				Infratentorial			Supratentorial			
	Mean	SD	N	Mean	SD	N	*P*	Mean	SD	N	Mean	SD	N	*P*	Mean	SD	N	Mean	SD	N	*P*
PIQ	85.4	20.1	16	98.4	13.6	15	0.035	96.7	17.6	15	107.0	15.7	15	0.17	99.3	21.3	15	109.2	11.3	15	0.18
VIQ	96.0	16.6	16	96.9	16.3	15	0.81	96.0	17.8	15	98.9	12.6	15	0.70	96.7	14.6	15	97.0	15.1	15	0.99
PS	76.8	17.4	11	89.6	22.3	13	0.13	84.4	22.3	11	94.9	21.4	13	0.17	89.5	24.1	10	102.1	24.6	12	0.11
Visual immediate	93.9	18.2	12	83.2	24.2	13	0.27	104.5	21.3	10	102.1	17.5	14	0.95	105.1	24.9	11	100.6	25.0	14	0.68
Visual delay	89.0	27.2	12	86.1	24.9	13	0.76	107.7	14.1	10	104.7	13.3	14	0.78	105.1	21.9	11	112.4	22.4	14	0.44
Verbal immediate	86.6	32.1	13	86.6	32.1	13	0.25	91.8	17.6	9	98.7	16.8	14	0.50	96.0	23.3	10	100.9	19.4	14	0.74
Verbal delay	87.4	19.6	10	87.8	29.5	13	0.85	96.7	18.1	9	96.2	18.1	14	0.94	96.9	22.8	10	102.9	17.5	14	0.54
General memory	84.0	21.4	10	90.2	24.1	13	0.35	97.9	21.7	8	101.6	19.7	14	0.52	100.9	31.5	10	106.8	20.6	14	0.64
Sky search	7.4	3.4	9	7.7	3.8	12	0.66	8.5	2.3	8	9.4	4.5	12	0.27	8.7	2.4	10	10.8	3.7	12	0.13
Score!	8.1	3.2	9	8.6	4.0	11	0.63	8.1	3.9	8	9.0	2.8	12	0.55	9.8	2.9	9	11.2	2.4	12	0.66
Sky search dt	4.4	4.0	8	6.6	3.3	11	0.17	5.3	3.1	8	6.4	2.9	12	0.44	5.3	4.0	9	8.2	3.7	12	0.84
Map mission	3.1	2.1	8	3.7	3.0	12	0.33	3.6	2.1	8	4.8	2.9	12	0.36	3.7	2.6	10	4.2	2.9	12	0.74
Reading	88.7	8.0	6	96.5	15.7	13	0.69	100.1	17.2	7	101.1	15.2	11	0.85	90.1	16.3	8	95.0	15.9	13	0.49
Maths	99.2	14.0	6	104.8	16.4	13	0.47	115.4	21.8	7	107.0	20.2	11	0.50	103.8	22.1	8	107.9	15.3	13	0.79
Spelling	89.2	6.9	6	93.9	13.8	12	0.093	102.1	17.8	7	94.2	13.3	11	0.21	91.4	18.0	8	97.5	15.7	13	0.36
Composite	90.5	9.2	6	96.3	15.9	12	0.65	105.5	20.1	7	99.7	16.9	11	0.24	93.6	19.8	8	99.7	16.9	13	0.54
	Hydrocephalus			No hydrocephalus				Hydrocephalus			No hydrocephalus				Hydrocephalus			No hydrocephalus			
	Mean	SD	N	Mean	SD	N	*P*	Mean	SD	N	Mean	SD	N	*P*	Mean	SD	N	Mean	SD	N	*P*
PIQ	88.2	18.7	22	100.2	14.5	9	0.076	98.9	15.7	21	108.9	19.4	9	0.19	99.7	17.6	21	114.7	12.6	9	0.037
VIQ	95.2	17.7	22	99.3	12.2	9	0.46	97.0	17.1	21	99.7	10.0	9	0.68	95.0	16.5	21	101.1	7.8	9	0.37
PS	77.4	16.6	17	99.3	22.9	7	0.024	82.2	20.0	16	105.9	17.7	8	0.02	89.5	22.7	16	114.7	21.2	6	0.011
Visual immediate	89.9	16.1	18	84.3	33.7	7	0.51	99.5	19.3	16	110.3	16.3	8	0.23	99.1	26.9	17	110.1	17.6	8	0.23
Visual delay	85.6	22.1	18	92.4	34.5	7	0.51	104.0	14.1	16	109.9	11.8	8	0.51	107.2	24.9	17	113.5	14.6	8	0.54
Verbal immediate	80.4	26.7	16	87.6	34.9	7	0.47	93.2	18.9	15	101.3	12.3	8	0.42	95.3	20.8	16	105.9	20.1	8	0.32
Verbal delay	85.0	21.1	16	93.6	33.8	7	0.41	95.5	19.1	15	98.0	15.8	8	0.82	95.6	20.4	16	110.1	14.8	8	0.13
General memory	80.9	20.9	16	102.4	20.4	7	0.04	97.5	22.1	14	105.1	15.9	8	0.38	100.1	26.3	16	112.8	22.1	8	0.24
Sky search	7.9	3.3	15	6.8	4.4	7	0.60	9.0	3.5	13	9.1	4.4	7	0.58	8.8	2.6	15	12.0	3.7	7	0.026
Score!	7.4	3.5	15	11.4	1.5	5	0.014	8.2	3.8	13	9.4	1.8	7	0.40	9.8	2.9	14	12.1	1.1	7	0.13
Sky search dt	5.0	4.1	14	7.6	0.9	5	0.20	5.5	3.0	13	6.7	3.0	7	0.40	6.1	3.9	14	8.6	4.0	7	0.16
Map mission	3.1	2.9	14	4.3	1.9	6	0.17	4.0	2.6	13	4.9	2.7	7	0.38	3.3	2.5	15	5.4	2.7	7	0.062
Reading	89.3	10.2	13	104.2	16.6	6	0.13	96.9	16.9	11	106.7	11.6	7	0.23	88.4	15.9	13	100.9	13.3	8	0.058
Maths	101.7	16.9	13	105.8	12.9	6	0.46	108.6	24.4	11	112.9	14.0	7	0.45	100.9	16.9	13	115.1	16.4	8	0.091
Spelling	88.1	10.5	12	100.8	10.6	6	0.31	96.6	17.7	11	98.3	11.5	7	0.72	91.5	17.8	13	101.1	12.7	8	0.13
Composite	89.5	11.9	12	104.2	13.6	6	0.25	96.0	26.9	11	106.7	8.2	7	0.22	91.7	19.7	13	106.5	9.4	8	0.077
	High grade			Low grade				High grade			Low grade				High grade			Low grade			
	Mean	SD	N	Mean	SD	N	*P*	Mean	SD	N	Mean	SD	N	*P*	Mean	SD	N	Mean	SD	N	*P*
PIQ	91.2	16.1	14	92.0	20.3	17	0.95	99.5	15.9	12	103.5	18.2	18	0.63	100.1	16.6	12	106.9	18.1	18	0.39
VIQ	94.9	18.1	14	97.7	14.8	17	0.67	98.0	13.4	12	97.6	16.6	18	0.85	93.5	16.1	12	99.1	13.5	18	0.35
PS	81.9	13.0	12	85.6	27.0	12	0.49	83.3	17.5	11	95.8	24.4	13	0.084	81.2	20.2	9	106.8	22.3	13	0.020
Visual immediate	88.2	12.3	12	88.5	28.4	13	0.98	98.3	18.1	10	106.5	19.1	14	0.32	94.4	29.2	11	109.1	18.7	14	0.092
Visual delay	93.3	12.1	12	82.1	33.2	13	0.21	107.2	7.1	10	105.1	16.8	14	0.93	111.3	26.1	11	107.6	19.1	14	0.63
Verbal immediate	86.4	19.0	12	78.4	37.3	11	0.33	94.9	19.9	10	96.8	15.4	13	0.78	94.7	23.4	11	102.3	18.4	13	0.45
Verbal delay	89.3	16.1	12	85.8	33.1	11	0.46	93.4	18.1	10	98.7	17.7	13	0.53	96.0	20.4	11	104.2	19.1	13	0.36
General memory	85.3	16.1	12	89.9	28.8	11	0.76	99.9	20.0	9	100.5	20.8	13	0.71	99.5	26.3	11	108.4	24.6	13	0.39
Sky search	6.5	3.4	10	8.5	3.6	11	0.83	7.3	3.3	8	10.3	3.6	12	0.84	8.3	3.1	9	10.8	3.1	13	0.48
Score!	7.8	3.5	9	8.9	3.7	11	0.31	7.6	3.6	8	9.3	2.9	12	0.27	9.8	3.5	9	11.2	1.8	12	0.32
Sky search dt	6.5	4.0	8	5.1	3.5	11	0.47	4.8	3.7	8	6.8	2.1	12	0.20	6.4	4.6	9	7.3	3.6	12	0.74
Map mission	3.3	1.9	10	3.6	3.3	10	0.83	4.3	2.3	8	4.3	3.0	12	0.84	3.4	1.7	9	4.3	3.2	13	0.48
Reading	95.9	16.7	11	91.4	9.7	8	0.52	97.6	19.1	7	102.7	13.4	11	0.33	92.6	17.4	10	93.6	15.2	11	0.85
Maths	98.9	16.5	11	108.6	13.0	8	0.17	108.6	13.0	8	117.4	18.7	11	0.011	111.7	17.7	11	111.7	17.7	11	0.13
Spelling	89.4	12.2	10	96.0	11.2	8	0.23	89.7	14.1	7	102.1	14.4	11	0.043	91.0	17.8	10	99.0	14.9	11	0.19
Composite	92.6	16.0	10	96.6	11.7	8	0.73	88.6	25.7	7	107.5	16.2	11	0.014	94.4	19.1	10	100.1	17.0	11	0.48

TABLE IV. Cognitive Results in Relation to Treatment Variables

	T1							T6							T12						
	Rx			No Rx				Rx			No Rx				Rx			No Rx			
	Mean	SD	N	Mean	SD	N	*P*	Mean	SD	N	Mean	SD	N	*P*	Mean	SD	N	Mean	SD	N	*P*
PIQ	92.0	19.6	22	91.0	15.6	9	0.77	101.2	19.4	20	103.4	12.4	10	0.78	100.5	19.5	20	111.8	9.5	10	0.120
VIQ	97.4	17.7	22	94.1	12.1	9	0.46	98.3	16.4	20	96.8	13.3	10	0.76	94.7	15.6	20	101.3	11.8	10	0.250
PS	81.4	20.2	18	90.7	22.9	6	0.35	87.9	23.8	19	98.2	12.1	5	0.16	89.0	23.3	16	116.0	16.9	6	0.009
Visual immediate	90.7	18.2	19	81.0	31.5	6	0.35	98.1	18.8	18	118.2	6.6	6	0.04	97.4	25.2	19	119.0	13.5	6	0.029
Visual delay	88.7	24.1	19	83.7	31.9	6	0.66	103.6	13.9	18	113.2	9.2	6	0.32	106.2	23.7	19	118.7	12.7	6	0.230
Verbal immediate	86.2	21.8	17	72.3	44.4	6	0.23	92.1	17.5	17	107.0	10.3	6	0.15	93.7	18.6	18	114.3	20.5	6	0.054
Verbal delay	88.6	20.3	17	84.8	38.0	6	0.78	91.4	17.6	17	110.7	7.1	6	0.04	93.7	17.4	18	120.5	10.5	6	0.006
General memory	84.9	22.8	17	94.7	22.7	6	0.07	93.3	18.8	16	118.8	7.2	6	0.07	97.3	24.0	18	125.3	16.3	6	0.010
Sky search	7.1	3.3	16	9.2	4.4	5	0.25	8.7	4.0	14	9.8	3.2	6	0.33	9.1	3.1	16	11.7	3.2	6	0.099
Score!	7.7	3.7	15	10.6	1.8	5	0.12	8.4	3.6	14	9.2	2.3	6	0.61	10.4	3.0	15	11.0	1.8	6	0.810
Sky search dt	5.2	3.8	14	7.0	3.1	5	0.30	5.1	3.0	14	8.0	1.7	6	0.07	6.0	4.4	15	9.3	1.2	6	0.054
Map mission	2.8	2.0	15	5.4	3.6	5	0.13	4.1	2.0	14	4.0	4.8	6	0.44	3.7	2.7	16	4.7	2.7	6	0.400
Reading	94.0	15.8	15	92.5	4.4	4	0.69	99.1	16.2	13	105.0	14.0	5	0.29	91.1	16.6	16	99.6	12.3	5	0.250
Maths	102.3	17.3	15	105.5	6.5	4	0.50	108.7	23.4	13	114.4	11.5	5	0.42	103.1	18.4	16	116.6	11.7	5	0.160
Spelling	90.9	13.1	14	97.5	4.7	4	0.19	93.9	14.2	13	106.0	15.6	5	0.06	91.4	4.7	16	107.4	12.4	5	0.028
Composite	93.9	16.0	14	96.3	1.7	4	0.60	96.2	23.5	13	110.6	13.9	5	0.08	93.4	17.7	16	110.2	12.3	5	0.069
	Chemo			No chemo				Chemo			No chemo				Chemo			No chemo			
	Mean	SD	N	Mean	SD	N	*P*	Mean	SD	N	Mean	SD	N	*P*	Mean	SD	N	Mean	SD	N	*P*
PIQ	89.6	15.3	11	92.9	20.0	20	0.66	95.9	13.3	9	104.5	18.3	21	0.29	92.0	13.5	9	104.5	16.6	21	0.020
VIQ	90.5	15.9	11	99.7	15.8	20	0.13	93.7	15.1	9	99.5	15.2	21	0.45	89.3	16.0	9	100.1	13.0	21	0.100
PS	78.7	15.6	10	87.4	23.7	14	0.21	75.8	17.3	8	97.3	21.0	16	0.01	76.9	16.3	7	105.5	22.7	15	0.013
Visual immediate	86.4	14.3	10	89.7	26.0	15	0.62	94.9	18.9	7	106.5	18.1	17	0.23	83.3	29.1	8	111.7	16.1	17	0.002
Visual delay	90.8	14.5	10	85.3	31.1	15	0.61	103.4	11.5	7	107.0	14.3	17	0.64	34.3	103.3	8	112.0	13.7	17	0.390
Verbal immediate	77.2	14.7	10	86.7	36.3	13	0.35	80.4	17.1	7	102.8	12.2	16	0.03	83.1	17.9	8	106.7	17.7	16	0.020
Verbal delay	82.5	16.3	10	91.5	30.3	13	0.37	83.6	17.1	7	102.0	15.2	16	0.06	85.0	18.8	8	108.1	15.4	16	0.013
General memory	78.3	17.7	10	94.5	24.1	13	0.25	87.0	23.2	6	105.3	16.8	16	0.01	86.6	26.8	8	113.2	19.7	16	0.009
Sky search	6.7	3.5	9	8.3	3.6	12	0.39	7.4	3.7	7	9.9	3.5	13	0.21	7.9	3.0	7	10.7	3.1	15	0.110
Score!	7.9	3.7	8	8.8	3.6	12	0.45	6.9	3.1	7	9.6	13.0	13	0.08	9.7	3.7	7	11.0	2.0	14	0.390
Sky search dt	5.4	4.1	7	5.8	3.6	12	0.90	4.0	3.3	7	7.0	2.2	13	0.11	5.6	5.4	7	7.6	3.1	14	0.330
Map mission	3.4	2.1	8	3.5	3.0	12	0.55	4.1	2.6	7	4.4	2.8	13	0.97	3.0	1.7	7	4.4	3.0	15	0.270
Reading	94.0	19.5	9	94.0	7.5	10	0.81	101.0	24.1	5	100.6	12.1	13	0.86	87.6	21.3	7	95.9	12.3	14	0.210
Maths	97.6	19.2	9	107.9	9.9	10	0.14	109.0	27.9	5	110.8	18.5	13	0.77	96.0	18.8	7	111.5	15.4	14	0.055
Spelling	87.8	14.4	8	96.0	8.7	10	0.15	92.0	16.8	5	99.3	14.7	13	0.22	87.7	21.3	7	98.9	12.7	14	0.086
Composite	90.3	18.9	8	97.7	8.1	10	0.38	100.0	24.5	5	100.2	21.8	13	0.94	88.6	22.7	7	101.8	13.7	14	0.120

Chemotherapy. Significant main effects of chemotherapy were identified in relation to processing speed ($P = 0.023$), visual immediate memory ($P = 0.033$), verbal immediate ($P = 0.014$) verbal delayed ($P = 0.024$), and General memory scores ($P = 0.018$). At individual time points, patients with BTs who received chemotherapy had significantly lower PIQ compared to those who did not at T12 ($P = 0.020$), and Visual immediate memory scores at T12 were significantly lower in patients with BTs who received chemotherapy than those who did not ($P = 0.002$). There were no significant differences between patients with BTs who received chemotherapy, and those who did not, with respect to attentional measures or the Wechsler Quicktest (Table IV).

Impact of age and gender. There were no significant differences amongst the patients with BTs aged <10 and >10 years on measures of PIQ, VIQ, attention or academic abilities. Group differences were seen for processing speed at T6 ($P = 0.020$); for visual immediate memory and GMI at T12 ($P = 0.012, 0.037$); and for selective attention (Map Mission) at T12 ($P = 0.020$), children aged >10 years performing more poorly than younger children at T12. There were no significant differences between males and females on most cognitive measures, exceptions being processing speed, spelling and the composite academic score at T6, on which males performed significantly more poorly than females ($P = 0.021$).]

DISCUSSION

To our knowledge, this is the only study to compare cognitive function in BT children and healthy controls prospectively early post-diagnosis. Pediatric patients with BTs have significantly reduced performance early after diagnosis on measures of PIQ,

processing speed, verbal and visual memory, and selective attention, highlighting the importance of early cognitive assessment and, when appropriate, pro-active provision of remedial educational support [7]. It is hoped that in the future it will also be possible to offer targeted cognitive remediation to children showing early evidence of cognitive impairment, with the aim of enhancing neuronal plasticity and improving ultimate outcome.

In the absence of pre-morbid data, comparison of BT children with matched normal controls is a more sensitive method of assessing the impact of BT and associated treatment than comparison with population norms. Cognitive performance may be reduced related to pre-morbid functioning while remaining within standardized norms [32]. We decided not to undertake pre-surgery assessments because of associated practical difficulties, including the need for urgent surgery, difficulties securing co-operation and concerns that motivation would be negatively impacted by anxiety [9]. A recent study which did investigate pre-treatment neuropsychological deficits in BT children found that at presentation 12% had full scale IQ (FIQ) scores <1 standard deviation (SD) below the normal average level; a further 6% had FIQ scores <2 SD below average [33], illustrating the impact of tumor and tumor-related factors upon cognition.

Improved cognitive performance over the first year post-diagnosis was seen in our patients with BTs with regard to PIQ; processing speed; visual and verbal immediate and delayed memory; and selective and sustained attention. Improved performance in controls was also seen for some tests, although not verbal delayed memory and sustained attention. Some of the change with time in patients with BTs presumably represents a practice effect, additional to recovering cognitive function. Significant deficits in cognitive performance in patients with BTs compared to controls were seen 1 year post-diagnosis for VIQ; processing speed, visual and verbal immediate memory, and selective attention. These results are in keeping with the results of studies of long-term outcome in childhood patients with BTs [4–6].

It is unclear why PIQ appears to recover following early assessment, whereas VIQ is stable following diagnosis and surgery and subsequently tails off between T6 and T12. A possible explanation is that performance IQ has been adversely affected by the visual and neurological deficits present in the BT cohort early after diagnosis and surgery, which tended to improve over time. The decline in performance of the BT group over time on measures of verbal intelligence may reflect the failure of the BT cohort to acquire new verbal skills at the appropriate rate, rather than representing loss of previously acquired knowledge [28].

The decision not to attempt to measure cognitive function pre-operatively means we cannot comment on the impact of surgery *per se*. In addition, investigation of multiple tumor-related variables was limited due to relatively small patient numbers, which also precluded undertaking a multivariate analysis. Within these limitations, however, our data suggest that infratentorial site, high tumor grade, and hydrocephalus are associated with worse cognitive outcomes. The impact of post-fossa syndrome, with associated cerebellar mutism is unclear due to the inclusion of only two patients that were affected.

Tumor location in the cerebral hemispheres, rather than the posterior fossa, has been associated with worse cognitive outcomes at baseline and following treatment in several studies [28,30,33,34]. However, other studies of children with cerebellar astrocystomas have identified abnormalities of cognitive processing, short-term memory and executive function, indicating the influence of the cerebellum on non-motor aspects of learning [35–37]. We have previously reported infratentorial tumors to be associated with significantly poorer health-related quality of life (HRQL) than suprtatentorial tumors [7]. However, with respect to cognitive outcome, we found few differences between infra- and supratentorial tumors, apart from performance IQ at T1, which was lower in children with infratentorial tumors.

For many years, hydrocephalus was not considered a significant risk factor for neuropsychological difficulties [10], early studies having failed to demonstrate an association between hydrocephalus and cognition in patients with BTs [10,38,39]. Our results suggest than hydrocephalus is associated with early cognitive impairment, a finding in keeping with data from recent long-term follow-up studies [30,35,40].

Almost two-thirds of our patients with BTs underwent CRT in the first year post-diagnosis. Those who underwent CRT had significantly lower scores at 12 months on tests of information processing and visual and verbal memory, although group differences for intellect and attention were not significant. CRT clearly remains a significant risk factor for cognitive impairment. CRT is recognized to produce a progressive decline in cognitive abilities [41] and it seems likely that differences between patients with BTs in our study who did or did not receive CRT are likely to increase over time. We are aware that academic ability has been identified as disproportionately affected in a large prospective study patients younger than 7 years, treated with CRT for medullobastoma [42]. Unfortunately a lack of an effect of age may be due to the reduced sample size in our study.

Patients who received chemotherapy had significantly lower scores 12 months post-diagnosis scores for PIQ and immediate measures of visual and verbal memory than those who did not. Concerns over chemotherapy toxicity have been increasing in the basic science and clinical literature [10,43,44]. A meta-analysis of 13 studies of cognition following chemotherapy-only treatment for pediatric acute lymphoblastic leukemia concluded that intellectual functioning is adversely affected, especially in the realms of perceptual reasoning, working memory and processing speeds [45]. The adverse effects of radiation and chemotherapy may be cumulative [41,46,47].

This study had a number of limitations, namely the relatively small numbers involved, which limited its power; the heterogeneous nature of the patient population with respect to tumor type and age; and the short duration of follow-up. Nevertheless, the results have demonstrated the feasibility of early serial cognitive testing in BT children and have shown evidence of early impairment, with recovery in some domains but not others. Future studies are required to replicate these results in larger numbers and to investigate the role of early rehabilitation strategies in improving cognitive outcome and QoL [12,48].

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