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Language outcomes subsequent to treatment of brainstem tumour in childhood

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Abstract. While the occurrence and management of brainstem tumours in children would not traditionally indicate potential direct structural impact on classical language centres, recent theories have implicated some involvement of the brainstem in a functional language and cognitive neural loop between the cerebellum and the cerebral hemispheres. Thus, the present paper explored the impact of treatment for brainstem tumour on the general and high-level language abilities of six children treated for brainstem tumour, in addition to phonological awareness skills. Group analysis revealed that children treated for brainstem tumour demonstrated intact language and phonological awareness abilities in comparison to an age- and gender-matched control group. Individual analysis revealed only one of six children treated for brainstem tumour revealed evidence of language disturbances, with an additional child demonstrating an isolated mildly reduced score on one phonological awareness task. Language deficits identified in a child treated with a combination of both radiotherapy and chemotherapy were noted in the high-level language area of lexical generation. Findings highlighted that no overt language disturbances were evident in children treated for brainstem tumour. However, further analysis into higher-level language skills in the present study indicated that both general and high-level language abilities require long-term monitoring in this population.

Keywords: Language, brainstem, tumour, children

1. Introduction

Tumour formation within the brainstem accounts for 10–20% of all central nervous system tumours in the paediatric population [11,12,22,33,41,51,53,58]. They frequently arise from the pons, and infiltrate the midbrain, medulla, the cerebellum and/or the fourth ventricle [4,7,8,11,12,22,33,41,51,53,58]. The potential for these tumours to have an impact on language function has been recently highlighted, with authors proposing theoretical involvement of the brainstem in cognitive and language function.

Leiner and colleagues [31] described the participation of the brainstem in the neural network of information passing from the cortex to the cerebellum. They outlined that the descending projection of nerve fibres from Broca's area in the cerebral cortex extends to the red nucleus which sends its major output to the inferior olive in the brainstem. In turn, the inferior olive is connected to the dentate nucleus, which is connected back to the red nucleus [31]. Thus, according to Leiner et al. [31] a neural loop exists within the brainstem in which the red nucleus receives a projection from language areas of the cerebral cortex. This neural loop is, therefore, proposed to participate in both language and motor functions: in the cognitive processes of word-finding, and the motor processes of expression; thereby functioning as a language-learning loop [31]. Leiner et al. [31] also described a larger projection than that from the cerebral cortex to the red nucleus. That is, a cortical projection to the pontine nuclei in the brainstem, which also send information to the cerebellum [31], previously established to be involved in language and cognitive function. This proposed role played by the brainstem in the pathways involved in language, therefore, highlights the potential for language impairment when tumours of the brainstem arise and are treated in childhood.

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Schmahmann [43] also attributed importance to the brainstem in the cerebrocerebellar circuit involved in language function. He outlined that input from brainstem structures that contain serotonin-, norepinephrine-, and dopamine are a substantial source of cerebellar afferents involved in this circuit. The involvement of the brainstem in an adaptive control system model relating to information representation and processing was also discussed by Parkins [40].

According to Lalonde and Botez-Marquard [29], the influence of the brainstem in cerebellar-related disorders accounts for signs such as transitory mutism and subsequent dysarthria following removal of midline cerebellar tumours. Additionally, patients who present with severe atrophy of the brainstem have been noted to have significant recall deficits in auditory verbal learning tests [29]. Difficulties have also been noted in patients with combined cerebellar and brainstem damage on neuropsychological tests involving recall and sorting when compared to patients with selective cerebellar damage who did not exhibit difficulties. However, no difference was found in four mental tests by heredodegenerative ataxia patients irrespective of the presence of pontine damage [29]. Lalonde and Botez-Marquard [29] believed that such results suggested a test-selective involvement of the brainstem in the neuropsychological deficits seen subsequent to cerebellar atrophy. Barone et al. [5] also indicated that evidence of the role of the brainstem (as with the cerebellum) in the acquisition of non-motor cognitive functions, such as verbal and performance intelligence, verbal learning, visuospatial memory and organization, has been accumulating.

As previously outlined, the most extensive studies into the communication abilities of children following treatment for brain tumour to date have been carried out by Murdoch, Hudson, and colleagues [24–26,35–38]. In examining the language abilities of twenty children who had been treated for posterior fossa tumour, Murdoch and Hudson-Tennent [38] documented the only known reported case in which the language abilities of a child with brainstem involvement have been reported. In the reported case, the tumour (an ependymoma) was located in the vermis, but extended downwards into the brainstem. The patient underwent subtotal surgical removal at the age of two years one month, at which time a ventriculoperitoneal shunt was also inserted, due to the presence of obstructive hydrocephalus. Following surgery, both radiotherapy and chemotherapy were administered [38]. Chemotherapy involved eight cycles of CCNU (Lomustine) (40 mg on day 1), procarbozine (50 mg daily on days 8–21), and vincristine (7 mg on days 8 and 29). Following treatment, this participant was considered cured as no evidence of residual tumour existed on a CT scan.

Findings from language assessments of this child revealed performance within the average range on measures of general language abilities [38]. However, performance in the *Sentence Combining* subtest of the Test of Language Development – Intermediate was considered more than one standard deviation below the mean. Results also indicated above average ability on tests examining rapid language retrieval and production, and confrontation naming. With the exception of one out of five sections (Part IV) which was considered below the normal range, the child also performed within the normal limits on an assessment of auditory comprehension. Although these specific impairments were noted, Murdoch and Hudson-Tennent [38] concluded in their study that this case demonstrated relatively intact language skills subsequent to treatment for a posterior fossa tumour with brainstem involvement.

The case reported by Murdoch and Hudson-Tennent [38] is the only report to date in which the language abilities of a child with a brain tumour involving the brainstem have been documented. In light of the more recently developing theories regarding the potential role of the brainstem in language, it would follow that a more thorough investigation of the language abilities of children subsequent to treatment for a brainstem tumour is required. It is also noted that while the test battery used by Murdoch and Hudson-Tennent [38] included one test of high-level language (the Test of Language Competence), the participant with brainstem involvement attempted but was unable to complete this assessment due to extreme difficulty understanding the requirements of each subtest. Therefore, potential difficulties in higher-level language processing may have gone undetected in this case. Particular investigation of the high-level language abilities in this group of subjects remains crucial given the documented impairment in high-level abilities in children with acquired brain injury [14,15,27] and the reported effects associated with treatment for childhood brain tumour [35]. Information is, however, particularly lacking in this area.

In addition to a comprehensive investigation of high-level language abilities in children treated for brainstem tumour, phonological awareness skills providing a foundation for literacy development have not previously been addressed, and therefore deficits in this area may have also been overlooked. The investigation in the present paper will, therefore, examine both the general and high-level language and pre-literacy abilities of children who have received treatment for a brainstem tumour in order to investigate the existence of language impairment.

2. Methodology

2.1. Participants

Six participants, 4 female and 2 male, ranging in age from 5 years 6 months to 14 years 11 months (mean age = 9.51 years; standard deviation = 3.59 years), who had completed treatment for a brain tumour involving the brain stem 6 months or more previously were included in the study. Four of the 6 participants were managed and treated at the Mater Children's Hospital in Brisbane, Australia, with the remaining two participants managed and treated at the Royal Children's Hospital, Brisbane, Australia. All participants included were recruited through the respective Haematology/Oncology departments of the above hospitals. Biographical details of the participants are summarized in Table 1. Six control participants individually matched for age and gender (mean age = 9.50 years; standard deviation = 3.56 years) were also included in the study, all of whom had no previous history of cancer, acquired brain injury, epileptic activity or seizures or speech/language difficulties.

All experimental and control participants spoke English as their first and only language.

2.2. Procedure

Language testing was carried out by the first author over a number of sessions in each participant's home, to reduce the influence of fatigue for the child. Both Case 1 and 2 underwent the first assessment session in hospital-based accommodation (provided for families who live outside the local area) and a quiet office in the hospital ward, respectively, with each of the second sessions carried out at the participants' homes. While the order was randomized to prevent fatigue effects the test battery was divided into two sections: 1) general language and 2) high-level language and pre-literacy.

2.2.1. General language assessments

Each of the 6 participants and their age- and gender-matched peers were administered three assessments of general language: either the *Clinical Evaluation of Language Fundamentals – Third Edition* (*CELF-3*) [44] or the *Clinical Evaluation of Language Fundamentals – Preschool* (*CELF-P*) [57], the *Peabody Picture Vocabulary Test – Third Edition* (*PPVT-III*) [18], and the *Hundred Pictures Naming Test* (*HPNT*) [19]. The age of each participant at the time of testing determined whether they were administered the CELF-3 or the CELF-Preschool. Five participants and their matched controls were administered the CELF-3 (for children aged 6+ years of age).

2.2.2. High-level language and phonological awareness assessments

Five of the 6 participants (Case 1, 2, 4, 5 and 6) (mean age = 10.32 years; standard deviation = 3.35 years) and their corresponding age- and gender- matched peers (mean age = 10.28 years; standard deviation = 3.35 years) were administered three assessments of high-level language and one assessment of phonological awareness. The following tests were included in the test battery: *Test of Problem Solving – Elementary, Revised* (*TOPS-Elementary*) [60] or *Test of Problem Solving – Adolescent* (*TOPS-Adolescent*) [59], *Test of Word Knowledge* (*TOWK*) [56], *Test of Language Competence – Expanded Edition* (*TLC-E*) [55], and either the *Queensland University Inventory of Literacy* (*QUIL*) [16] or the *Test of Phonological Awareness* (*TOPA*) [52]. Again, the age of each participant treated for brainstem tumour and their individually matched peer determined the version or age-group level that was completed for each assessment.

While assessments of high-level language were not administered to Case 3 as this participant was too young to complete these assessments, the pre-literacy assessment, the Test of Phonological Awareness (TOPA), was carried out to determine the level of phonological awareness abilities. Case 3 was administered this assessment as she was below the school-age limit of the QUIL assessment administered to the remaining 5 participants treated for brainstem tumour. Therefore, as Case 3 was the only participant to complete this assessment the TOPA was not included in the group statistical analysis. However, these results are discussed in the individual case analyses.

Table 1

Biographical data of participants treated for brainstem tumour

Case	Gender	Age[a] at assessment	Age[a] at diagnosis	Time[a] post treatment	Tumour type	Tumour location	Treatment	Extent of Surgery	Total Radiation Dosage	Chemotherapy drugs
1	F	10;5	8;7	1;6	LG Astrocytoma	Lower BS/upper CM	R	–	54Gy	–
2	F	11;11	9;11	2;10	LG Astrocytoma	Right pons	R	–	54Gy	–
3	F	5;6	2;5	2;4	Ependymoma	Third ventricle & BS	S, R, C,	subtotal	NA	cisplatin, etoposide, vincristine.
4	F	14;11	8;8	6;3	LG Astrocytoma	Medullopontine angle	S	total	–	–
5	M	6;7	1;8	2;0	Glioma	BS	R, C	–	54Gy	tamoxifen, CCNU, etoposide.
6	M	7;8	5;5	0;6	LG Astrocytoma	Lower BS/upper CM	S,C	subtotal	–	vincristine, carboplatin

Note: [a]Age and time presented in years and months; LG = low-grade; BS = brainstem; CM = cervico-meduallry; S = surgery, R=radiotherapy; C = chemotherapy; NA = not available; – not applicable; Gy = grays.

Table 2

Brainstem tumour and control group analysis: Means (M), standard deviations (SD), and Mann Whitney U comparisons for the Clinical Evaluation of Language Fundamentals – Third Edition/Preschool (CELF-3/Preschool), Peabody Picture Vocabulary Test – Third Edition (PPVT-III), and the Hundred Pictures Naming Test (HPNT)

Parameter	Brainstem group ($n = 6$)		Control group ($n = 6$)		Mann Whitney	Asymp. Sig. (2-tailed)
	M	SD	M	SD	U	
CELF-3/Preschool						
Receptive language score	118.50	10.13	114.67	7.23	12.0	0.33
Expressive language score	108.67	9.35	118.00	7.24	7.0	0.08
Total language score	113.67	7.61	116.50	6.78	15.5	0.69
PPVT-III	106.67	6.56	111.00	12.20	14.0	0.52
HPNT	96.00	3.63	97.17	2.93	6.5	0.65

Note: p significant at < 0.05.

Table 3
Brainstem tumour and control group analysis: Means (M), Standard deviations (SD), and Mann Whitney U comparisons for the Test of Problem Solving (TOPS), Test of Word Knowledge (TOWK), Test of Language Competence - Expanded (TLC-E), and Queensland University Inventory of Literacy (QUIL)

Parameter	Brainstem group ($n = 5$)		Control group ($n = 5$)		Mann Whitney U	Asymp. Sig. (2-tailed)
	M	SD	M	SD		
TOPS	107.40	10.78	108.60	13.13	12.5	1.00
TOWK						
Receptive composite	106.60	10.04	110.20	10.09	10.0	0.60
Expressive composite	107.60	8.44	107.80	17.44	11.5	0.83
Total score	107.40	9.18	109.60	12.70	12.0	0.92
TLC-E						
Interpreting intents	102.40	10.48	106.40	16.99	12.0	0.92
Expressing intents	100.60	14.91	109.60	14.29	6.5	0.21
Total score	101.40	11.33	109.60	16.43	8.0	0.34
QUIL						
Nonword spelling	14.80	2.17	12.00	2.94	3.5	0.10
Nonword reading	12.60	2.97	9.75	3.86	7.0	0.45
Syllable identification	12.00	1.41	10.50	1.29	4.5	0.16
Syllable segmentation	11.40	1.95	10.2	1.26	5.5	0.25
Spoken rhyme	11.80	1.30	8.50	3.70	1.5	0.03
Spoonerisms	12.40	2.97	11.50	1.73	9.0	0.80
Phoneme detection	10.60	2.79	10.50	2.08	9.0	0.80
Phoneme segmentation	14.40	0.89	13.25	2.63	5.5	0.26
Phoneme manipulation	12.80	1.79	10.50	3.32	5.0	0.21

Note: p significant at < 0.05 for TOPS, TOWK, and TLC-E; p significant at < 0.01 for QUIL.

3. Results

Two levels of analysis were employed to determine the presence of language disturbances in a group of children treated for brainstem tumour consistent with previous research methodology [38]. The first level involved a statistical comparison between a group of participants treated for brainstem tumour and the group comprised of individually matched peers. The second level of analysis involved a comparison of the individual standard scores of each participant treated for brainstem tumour to the normative data provided for each assessment, accounting for any individual variability and potential individual language disturbances that may have been overlooked in the statistical group level comparison. Due to the heterogeneity of participants, this level of analysis allowed an examination of the language outcomes of each participant treated for brainstem tumour in the context of individual tumour presentations, treatments, age at diagnosis and treatment, presenting symptoms, time post treatment at which language testing occurred, and any other significant individual features.

3.1. Group analysis

Homogeneity of variance was tested across all parameters using the Levene's Test for Equality of Variance, and was found to be non-significant ($p > 0.05$). However, due to small group numbers conservative analysis using non-parametric statistics was conducted. Therefore, the Mann-Whitney U test was employed to determine the presence of statistically significant discrepancies across all parameters. Due to the multiplicity of subtests comprising the QUIL, a stringent alpha level of $p < 0.01$ was applied for this assessment only [46]. For all other tests an alpha level of 0.05 was adopted.

Due to the variation in age level across participants ranging from 5 years 6 months to 14 years 11 months, two different general language assessments, the CELF-Preschool and the CELF-3, were completed according to age, with differing age level subtests. Despite two versions of the general language assessment having been completed, the data was able to be collapsed as the CELF-Preschool was designed as a downward extension of the original Clinical Evaluation of Language Fundamentals – Revised (CELF-R) [45]. Subsequent to publication of the CELF-Preschool, the CELF-R was again revised and published as the Clinical Evaluation of Language Fundamentals – Third Edition (CELF-3), the version used for the older children in the present study. Consequently, group statistics at a subtest level was not possible, with only overall and total scores compared in the group analysis.

Table 4
Individual general language assessment results (represented in standard scores) of Cases 1, 2, 4, 5, and 6 treated for brainstem tumour on the Clinical Evaluation of Language Fundamentals – Third Edition (CELF-3), Peabody Picture Vocabulary Test – Third Edition (PPVT-III), and the Hundred Pictures Naming Test (HPNT)

Tests	Case 1	Case 2	Case 4	Case 5	Case 6
CELF-3					
Receptive Language	131	125	104	125	112
Concepts and directions	17	12	8	16	16
Word classes	15	15	9	13	13
Semantic relationships[b] / Sentence structure[a]	12[b]	15[b]	15[b]	13[a]	7[a]
Expressive language	120	106	116	104	114
Formulated sentences	12	12	15	12	15
Recalling sentences	12	12	13	10	9
Sentence assembly[b] / Word structure[a]	16[a]	9[b]	10[b]	10[a]	13[a]
Total language	126	116	110	115	113
PPVT-III	101	102	118	102	110
HPNT (Raw score/100)	97	99	100	94	96

Note: [a] = Level 1 subtest variation; [b] = Level 2 subtest variation; Standard scores in italics = normal range 85–115; Subtest standard score normal range = 7–13.

As norms were not calculated for Grade 1 aged children on the Visual Rhyme subtest of the QUIL, a standard score could not be calculated from the performance of Case 5. Therefore, as the performance of only four children constituted the group for this subtest, statistical tests could not be carried out. Group analysis of performance on the Visual Rhyme subtest is, therefore, not reported. However, it is included in the individual case analysis. Additionally, as both Case 4 and the matched control participant were aged above the upper limits of the normative data provided by the QUIL (Grades 1–7) in Grade 9, individual standard scores were calculated based on the Grade 7 normative data.

Subsequent to statistical analysis, it was determined that no significant differences ($p > 0.05$) were evident on measures of general language abilities between a group of 6 participants who had been treated for brainstem tumour and their individually matched peers (see Table 2). Statistical comparison also revealed that across performance on both the high-level language and phonological awareness assessments, the group of five participants (Cases 1, 2, 4, 5 and 6) treated for brainstem tumour were not significantly different ($p > 0.05$) to those of their age- and gender-matched control group across all subtests of the TOPS, TOWK, TLC-E, and the QUIL (see Table 3).

3.2. Individual analysis

An individual analysis revealed one of six cases with demonstrated reduced ability (Case 5) in some specific aspects of language function, and an additional participant noted to have an isolated weakness in one aspect of phonological awareness (Case 2). The remaining four participants were determined to function within normal limits on all parameters. The individual case presentations of all six children treated for brainstem tumour are presented in the following case analyses.

3.2.1. Case 1

Case 1 was diagnosed with a lower brainstem/upper cervical spinal cord low-grade astrocytoma (see Fig. 1), following investigations into a left sided hemi-atrophy, at the age of 8 years 7 months. No surgical resection or debulking of the tumour was carried out. A 6 week course of radical radiotherapy treatment (external beam radiation) was commenced one month later, with a dose of 54 Gy delivered in 30 fractions over the course of treatment. The absence of clinical signs and a series of follow-up Magnetic Resonance Imaging (MRI) scans over the next nine to twelve months (including a scan one day prior to language testing – see Fig. 2) demonstrated no evidence of tumour progression. Based on a number of thallium studies it was determined that the tumour was no longer viable, and that the disease was deemed stable.

Language testing for the study was carried out eighteen months following completion of radiotherapy treatment, at the age of ten years five months. Case 1 performed above the normal range for a child her age on a measure of general receptive and expressive language abilities (CELF-3), and on a confrontation nam-

Table 5
Individual high-level language and phonological awareness assessment results (represented in standard scores) of Case 1, 2, 4, 5, and 6 treated for brainstem tumour on the Test of Problem Solving (TOPS), Test of Word Knowledge (TOWK), Test of Language Competence – Expanded (TLC-E), and Queensland University Inventory of Literacy (QUIL)

Tests	Case 1	Case 2	Case 4	Case 5	Case 6
TOPS	102	107	123	94	111
TOWK					
Receptive composite	94	100	106	115	118
Synonyms[b]/ Word opposites[a]	8[b]	10[b]	12[b]	11[a]	12[a]
Figurative usage[b]/ Receptive vocabulary[a]	10[b]	10[b]	10[b]	14[a]	14[a]
Expressive composite	103	97	114	106	118
Word definitions	11	9	12	9	14
Multiple contexts[b]/ Expressive vocabulary[a]	10[b]	10[b]	13[b]	13[a]	12[a]
Total langrage	98	98	111	111	119
TLC-E					
Interpreting intents	88	97	115	103	109
Listening comprehension: Making inferences	8	11	10	13	12
Figurative language	8	11	15	8	11
Expressing intents	100	103	100	79[c]	121
Ambiguous sentences	9	11	11	6*	11
Oral expression: Recreating Sentences[b]/Speech Acts[a]	11[b]	10[b]	9[b]	7[a]	16[b]
Total langrage	93	100	108	89	117
QUIL					
Nonword spelling	15	16	16	11	16
Nonword reading	10	10	12	17	14
Syllable identification	11	11	11	14	13
Syllable segmentation	8	12	12	12	13
Spoken rhyme	11	11	11	14	12
Visual rhyme	12	12	12	*	11
Spoonerisms	11	13	12	17	9
Phoneme detection	10	6[c]	12	13	12
Phoneme segmentation	15	15	13	15	14
Phoneme manipulation	13	11	11	15	14

Note: [a] = Level 1 subtest variation; [b] = Level 2 subtest variation; [c] = below normal range (Standard scores in italics: normal range 85–115; Subtest standard score normal range = 7–13); * normative data not available for this child.

ing assessment (HPNT). Scores also within in the normal range on the PPVT – III highlight abilities that are commensurate with a child of similar age in the area of receptive vocabulary (see Table 4). Similarly, assessments of high-level language and phonological awareness revealed abilities that were considered within the normal range (see Table 5).

3.2.2. Case 2

Case 2 was diagnosed with a low-grade astrocytoma in the right pons extending into the middle cerebellar peduncle (see Fig. 3), after presenting with a 2 month history of poor balance, at the age of 9 years 11 months. The tumour was regarded as well differentiated. No surgical resection or debulking of the tumour was carried out. A 6-week course of radical radiotherapy treatment (external beam radiation) was commenced two months later. An overall dose of 54 Gy was delivered in 30 fractions over the treatment period.

Testing for the study was carried out 22 months following completion of radiotherapy treatment, at age 11 years 11 months to 12 years 0 months. While considerable reduction of the tumour was noted in the initial follow-up MRIs following radiotherapy, a MRI study carried out 3 weeks prior to testing (see Fig. 4) indicated that there had been no change in the size or appearance of the astrocytoma in the right middle cerebellar peduncle compared with the most recent study prior. A minimal mass effect was also found, but was restricted to right fourth ventricle. A thallium study

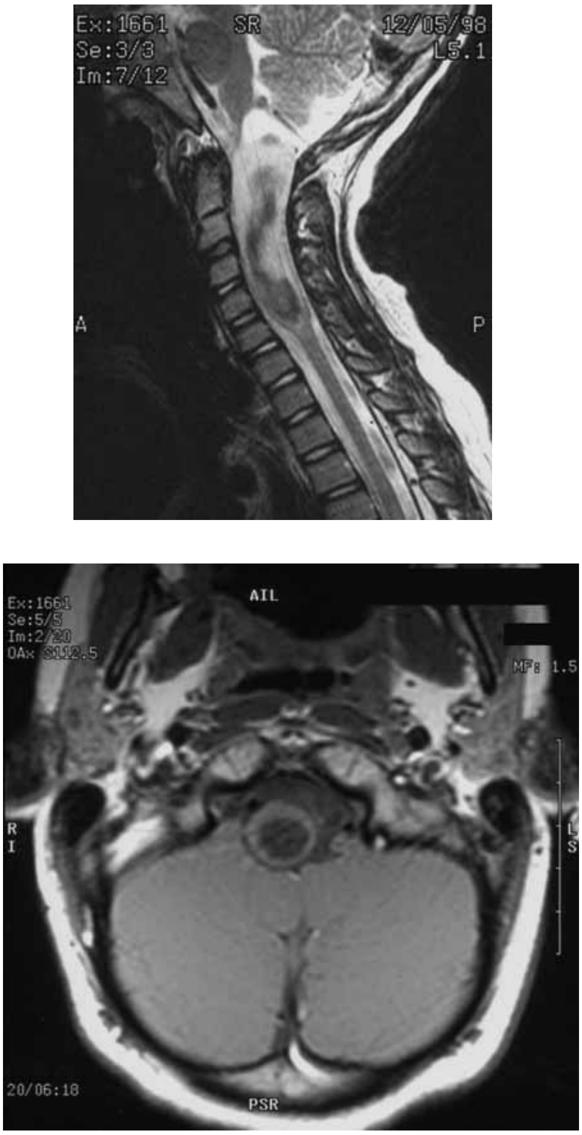

Fig. 1. *Case 1 at diagnosis*: Sagittal and coronal MRI scans indicating a lower brainstem/upper cervical cord low-grade astrocytoma. Report indicated a large intramedullary tumour mass expanding the cervical cord and extending from the level of C5/6 disc inferiorly to the caudal medulla.

carried out 6–9 months earlier indicated a non-viable tumour, deemed stable by the participant's oncologist.

Performance on the general language battery of tests revealed that Case 2 was positioned well within the normal range across all tests, including scores above the normal range on the Receptive Language component of the CELF-3, and on a test of confrontation naming (HPNT) (see Table 4). Case 2 performed well within the normal range across tests of high-level language

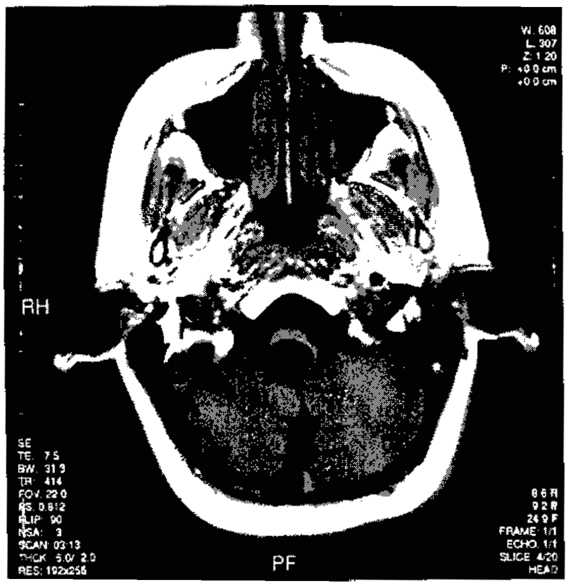

Fig. 2. *Case 1 at language testing* (*18 months post treatment*): T1 weighted coronal MRI scan of the brain post radiotherapy demonstrating a cystic astrocytoma in cervicomedullary junction.

and phonological awareness compared to the normative data provided for each assessment (see Table 5). While standard scores for nine of the ten phonological awareness subtests were either in the high average to above normal range for a child Case 2's age, performance on the Phoneme Detection subtest was noted to be below the normal range. This isolated subtest deficit indicated a difficulty detecting the word without the same first/end/last/middle sound as the remaining three words in the item.

3.2.3. Case 3

At the age of 2 years 5 months, Case 3 was diagnosed with an ependymoma involving both the third ventricle and the brain stem (see Fig. 5) following a 4 week history of vomiting, headache, and irritability. A 22 history of unsteady gait and ataxia was also present. Case 3 was also reported to have a history of head tilt to the right, as well as awakening and screaming out during the night. An emergency third ventriculostomy was performed to relieve hydrocephalus (of which papilloedema was also reportedly a symptom), with subtotal resection and ventriculoperitoneal shunt insertion 5 days later. Two weeks subsequent, chemotherapy commenced. Cycle 1 utilized cisplatin on day 1, with etoposide administered on days 1–21. This cycle was repeated. Cycle 3 utilized the agents cyclophosphamide, etoposide, and vincristine over 21 days. This cycle was also repeated. Radiotherapy

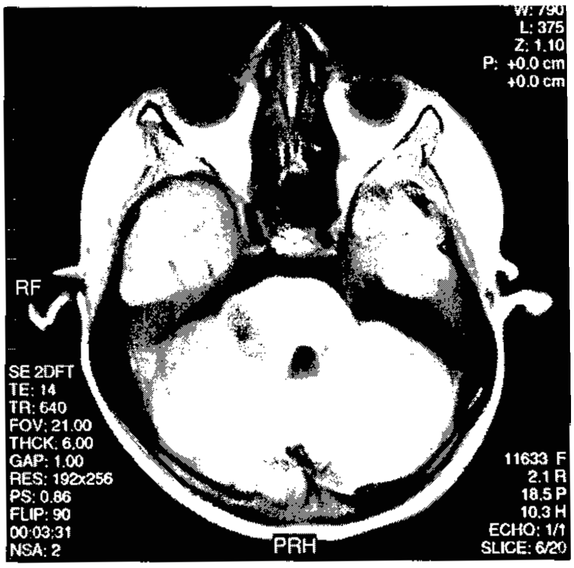

Fig. 3. *Case 2 at diagnosis*: T1 weighted coronal MRI scan revealing a 2 × 2 × 1.8 cm low-grade astrocytoma in far lateral aspect of pons extending into the right middle cerebellar peduncle. Mild mass effect with some effacement of the lateral ventricle.

treatment commenced approximately 3 weeks following completion of the chemotherapy regime (8 months subsequent to diagnosis). Posterior fossa irradiation was administered with a local field boost (details of exact dosage not available), twice daily over 5 weeks.

Language testing was carried out 2 years and 4 months following treatment completion, at the age of 5 years 6 months (see Fig. 6). Case 3 performed well within the normal range on general language tests across both receptive and expressive subtests on the CELF-Preschool. Additionally, confrontation naming skills were demonstrated to be above the normal range for a preschool aged child on the HPNT. A summary of Case 3's results are provided in Table 6. Although Case 3 was not administered assessments of high-level language, performance on the pre-literacy assessment, the TOPA, represented performance that was within the normal range with a standard score of 105.

3.2.4. Case 4

Case 4 was diagnosed at the age of 8 years 8 months with a low grade pontine astrocytoma, arising at the medullo-pontine angle posteriorly, extending into the fourth ventricle and involving the middle cerebellar peduncle on the right (see Fig. 7). A 3 year history of right VIth cranial nerve palsy was noted, along with a right VIIth cranial nerve palsy for 2 years. A CT head scan performed three years prior to actual diagnosis did

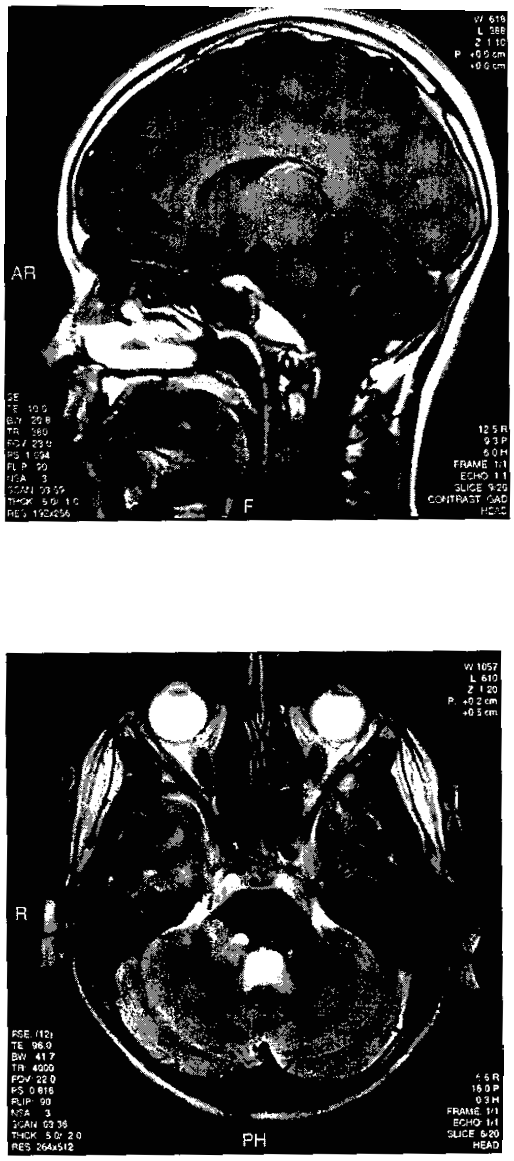

Fig. 4. *Case 2 at language testing* (*1 year 10 months post treatment*): Sagittal and coronal MRI scans demonstrating no interval change in size or appearance of previously demonstrated astrocytoma in right pons following radiotherapy treatment.

not reveal a tumour. Following diagnosis a total surgical excision was performed, leaving residual/persistent right-sided lower motor neurone VI and VII cranial nerve palsies. Dexamethasone was administered postoperatively.

Six years and 3 months post treatment, at the age of 14 years 11 months, Case 4 participated in language testing. A MRI study was carried out two days following language testing (see Fig. 8). Case 4 performed

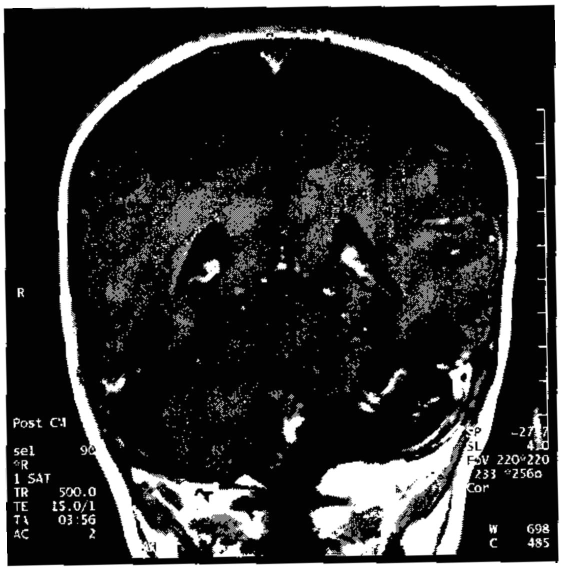

Fig. 5. *Case 3 at diagnosis*: Coronal and axial MRI scans demonstrating an ependymoma involving both the third ventricle and the brainstem.

within the normal limits on a measure of general receptive and expressive language abilities when compared with the standardized test normative data (see Table 4). Receptive vocabulary as assessed by the PPVT-III was considered intact, with a standard score above the normal range yielded. Confrontation naming was also considered to reflect ability in the normal range for a child Case 4's age. Case 4 also performed consistently within the normal range on assessments of high-level language and phonological awareness skills (see Table 5).

3.2.5. *Case 5*

Case 5 presented at the age of 20 months with a deterioration of balance and was diagnosed with a 3.2 cm brainstem glioma causing mild-moderate obstructive hydrocephalus (MRI scan unavailable). Chemotherapy was administered and the tumour was partially controlled with tamoxifen, then lomustine (CCNU) two years later, and etoposide the following year. Radiotherapy was commenced 2 years 10 months following diagnosis at the age of 4 years 2 months. Radical radiotherapy (external beam radiation) to the brainstem was administered using posterior oblique fields. A dose of 54 Gy was delivered in 30 fractions over 6 weeks. Dexamethasone was given at this time.

Language testing was administered at the age of 6 years 6/7 months (2 years following treatment). A MRI study carried out 1 month following testing revealed no interval change in the appearance of the tumour compared to a previous follow-up scan, and ventricular size and configuration within normal limits. Posterior fossa and supratentorial structures were also considered normal in appearance with no evidence of radiation necrosis (see Fig. 9). Case 5 had a history of speech pathology intervention following a referral 2 years subsequent to diagnosis. While general receptive language abilities were consistently deemed to be within normal limits, persisting word finding difficulties were noted in the area of expressive language.

In the present study, Case 5 performed within normal limits on a general measure of receptive and expressive language abilities (the CELF-3), compared to the standardized test normative data. Receptive vocabulary as measured by the PPVT-III indicated abilities in the normal range, with naming abilities on the HPNT found to be above the normal range for a child in Grade 1 at school. Case 5's results are summarized in Table 4.

While Case 5 performed in the high to above the normal range on an assessment of phonological awareness skills (QUIL), high-level language abilities reflected some areas of weakness (see Table 5). Although performance on both the TOPS-R Elementary and the TOWK fell within the normal range, high-level language abilities examined by the TLC-E (Level 1) were considered reduced in the Expressing Intents component, with performance falling below the normal range overall. This overall expressive score is also inclusive of the subtest, *Ambiguous Sentences*, which was also considered below the normal range. This subtest examines a child's ability to interpret sentences with ambiguities arising from multiple meaning words or phrases.

Table 6
General language assessments results (represented in standard scores) of Case 3 treated for brainstem tumour, on the Clinical Evaluation of Language Fundamentals - Preschool (CELF-Preschool), Peabody Picture Vocabulary Test - Third Edition (PPVT-III), and the Hundred Pictures Naming Test (HPNT)

Tests	Case 3
CELF-Preschool	
Receptive Language	114
Linguistic concepts	12
Basic concepts	13
Sentence structure	12
Expressive Language	94
Recalling sentences in context	10
Formulating labels	10
Word structure	7
Total language	103
PPVT-III	107
HPNT (Raw score/100)	90

Note: Standard scores *in italics* = normal range 85–115; Subtest standard score normal range = 7–13.

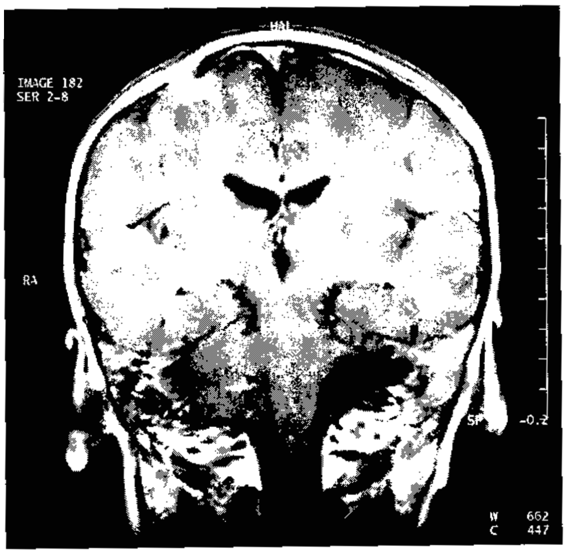

Fig. 6. *Case 3 at language testing* (*2 years 4 months post treatment*): Coronal and axial MRI scans indicating residual tumour in brainstem and cerebellum post surgery and chemotherapy treatment.

3.2.6. Case 6

Case 6 was diagnosed at the age of 5 years 5 months with a low grade cervicomedullary astrocytoma of the lower brainstem/upper cervical spinal cord region (diagnosis MRI scan unavailable), following a 6 month history of neck stiffness, and early morning vomiting for 6 to 8 weeks. A head tilt was also noted for 7 months prior, for which physiotherapy had been employed, in addition to a slight dysdiadochokinesia and some difficulties swallowing food. Hydrocephalus was not considered present. Partial resection and debulking of the tumour was carried out 2 months following diagnosis. Iatrogenic Cushing's syndrome was noted following surgery. A 10 week induction phase of chemotherapy was commenced 3 months subsequent to surgery with a weekly regime that utilized vincristine and carboplatin. On completion symptoms of diplopia and signs of bilateral VI cranial nerve palsy became evident. A planned maintenance program over 12–18 months commenced, while omitting one dose of carboplatin in Week 3 of each cycle, due to these symptoms.

Language testing was carried out 3 years and 3–4 months following diagnosis and 2 years 1–2 months following treatment completion, at the age of 7 years 8 months. A MRI study taken over 2 weeks following language testing showed little significant change of tumour within the cervical cord from the medulla to the level of T1 (see Fig. 10). Both general receptive and expressive language abilities as examined by the CELF-3 were noted to fall well within the normal range. Confrontation naming abilities were also considered to be in the normal range for a child Case 6's age, together with receptive vocabulary skills on the PPVT-III. Case 6's results are summarized in Table 4. Additionally, Case 6 performed in the high to above normal range across all assessments of high-level language abilities and phonological awareness (see Table 5).

4. Discussion

The results of a group level analysis failed to demonstrate a distinctive difference in the general language, high-level language, or phonological awareness abilities between a group of children who had received treatment for brainstem tumour and their age and gender matched peers. Except for some subtle high-level language disturbances in the area of lexical structures by Case 5, and isolated area of weakness in the literacy skills of Case 2 measured by the *Phoneme Detection* subtest of the QUIL, all participants demonstrated individual language abilities that were not considered significantly different when compared to the normative data provided for each standardized assessment. In certain instances, group means and some individual performances were in fact above the normal range.

Prior to this investigation, specific reports of language abilities following treatment for childhood brainstem tumour have not emerged, except for one case with brainstem involvement documented as part of a larger cohort of children with posterior fossa tumour investigated by Murdoch and Hudson-Tennent [38]. These researchers documented similar findings to the current group investigation, in reporting that no distinct, overt pattern of language impairment was evident. Findings obtained in the current study, in which larger numbers were present and a more comprehensive test battery was used than in testing the one participant with brainstem involvement in the study documented by Murdoch and Hudson-Tennent [38], suggests that language disturbances are not typically anticipated for this population at least in the short term, despite treatments including radiotherapy.

This in itself, however, is significant given the diversity of the brainstem tumours represented in the children in the present study, in size, specific location, characteristics, and accompanying symptoms and resulting effects, as well as the often intensive and individual treatment programs employed. It is also suggested that the prevalence of adverse effects such as language

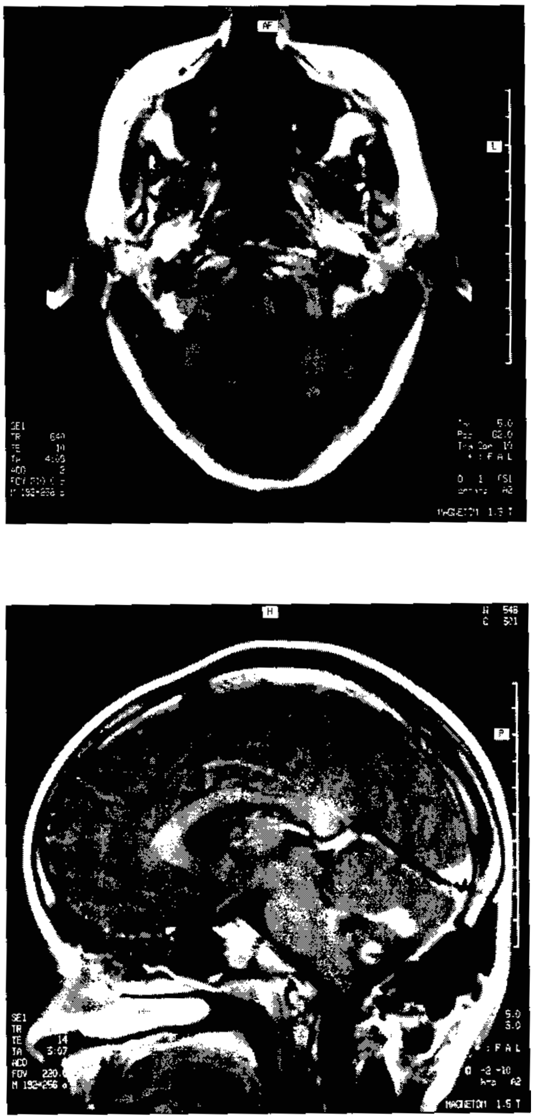

Fig. 7. *Case 4 at diagnosis*: Coronal and sagittal MRI scans indicating a pontine astrocytoma arising at medullopontine angle posteriorly. Extension into fourth ventricle and involvement of middle cerebellar peduncle on right.

disturbances, previously attributed to treatment techniques utilized in children treated for brain tumour may have less impact on long-term language and cognitive function of children treated for brainstem tumour than observed in other populations [24,26]. However, it is important to note that implications for children treated with cranial or posterior fossa radiotherapy may present many years following treatment, as documented effects related to treatment for brain tumour in children have been reported to occur up to as many as fourteen years

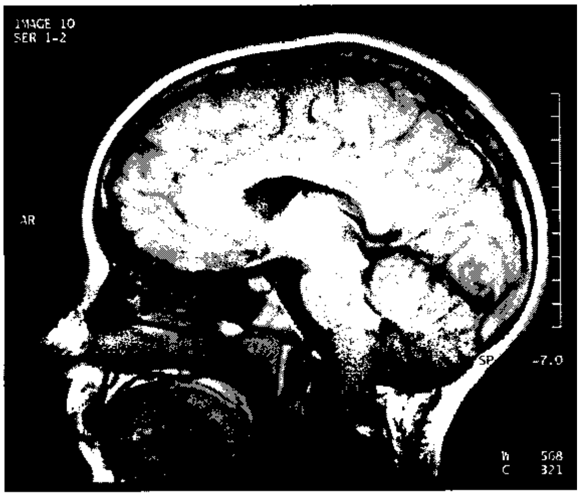

Fig. 8. *Case 4 at language testing* (*6 years 3 months post treatment*): Sagittal MRI scan demonstrating tumour stability post surgery treatment for brainstem tumour, with no progression or evidence of new disease.

following treatment [30,32]. Considering that most participants in the present study were only a few years post treatment, the issue of any long term treatment impact is as yet unexplored. More detailed investigation of the language abilities of children treated for brainstem tumour in the long-term is therefore required.

It was anticipated that areas of language weakness in the population of children treated for brainstem tumour may include the cognitive processes of word-finding and the motor processes of expression, which have been reported to result from a disturbance to the neural loop in the brainstem implicated in language function [31]. It has also been reported that tasks involving recall and sorting may also be affected post brainstem injury [29]. However, as no overt deficits were noted across the group analysis, disturbances to these processes termed the language-learning loop by Leiner et al. [31], do not appear to be evident. However, while word-finding was not considered impaired in the present study (with naming abilities of all participants measured by the Hundred Pictures Naming Test found to be intact) it must be acknowledged that Case 5 had a history of residual persisting word-finding difficulties for which speech pathology intervention was received. This history for Case 5 may therefore reflect some support for this previous report by Leiner and colleagues [31]. Additionally, while performance by Case 5 was also considered below the normal range on the Expressing Intents component of the TLC-E (Level) (including the *Ambiguous Sentences* subtest), at a group level no patterns of deficit emerged that were considered consistent

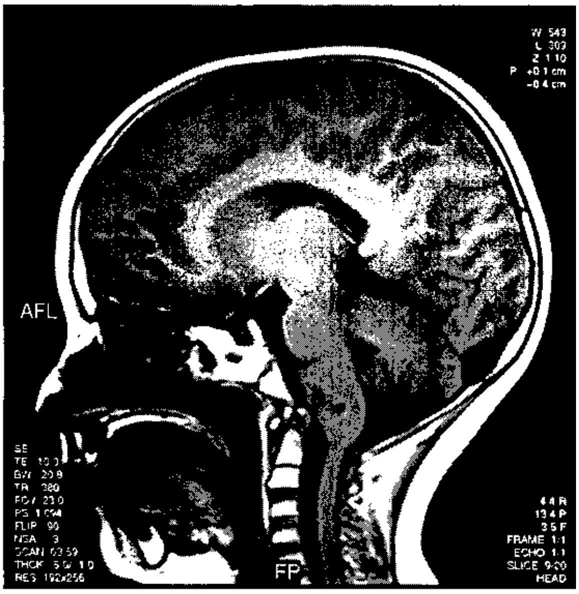

Fig. 9. *Case 5 at language testing* (*2 years post treatment*): Sagittal T1 weighted MRI scan post radiotherapy and chemotherapy treatment for brainstem glioma. Posterior fossa structures and supratentorial structures normal with no radiation necrosis.

with the hypothesized role of the brainstem in language processing [31].

At the level of individual analysis, a specific area of difficulty was noted in the performance of Case 5 on the expressive TLC-E subtest, Ambiguous Sentences, which involves a lexical component. Therefore, it was considered that Case 5 may have had some difficulty generating structures that involve lexical items. It is also suggested that earlier word-finding difficulties noted in the history of speech pathology intervention for this case, may suggest the disturbance of later lexical skills at a higher level. Other reports of language deficits following acquired brain injury have noted weaknesses in this area. A significant impairment was noted by Docking et al. [15] in the lexical component of an assessment of high-level language abilities administered to a group of nine adolescents with closed head injury in the area of linguistic humour. Additionally, Hudson and Murdoch [25] reported severe semantic-lexical deficits immediately post-treatment in children treated with both surgery and central nervous system radiation for a posterior fossa tumour, with some cases demonstrating persistent difficulties.

Although Murdoch and Hudson-Tennent [38] reported relatively intact language skills evidenced by their one participant treated for brainstem tumour, a number of subtle language characteristics were noted in their study. Specifically, Murdoch and Hudson-

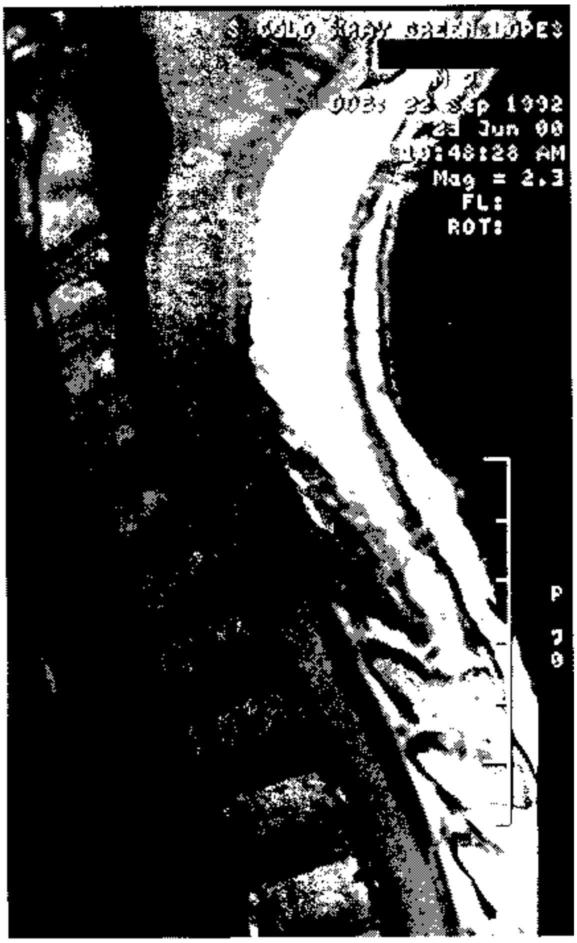

Fig. 10. *Case 6 at language testing* (*6 months post treatment*): Sagittal T1 weighted MRI scan demonstrating post-operative changes in posterior right aspect of upper cervical spine. Expansion and irregular enhancement within the cervical cord from medulla through to approximately T1 level consistent with primary cervical cord astrocytoma.

Tennent [38] noted a reduction in language performance in the obtained Speaking and Syntax Quotients in relation to the Listening and Semantics Quotients in their case, and was considered to be representative of the difficulties experienced in the Sentence Combining and Word Ordering subtests. Additionally, it was noted by these authors that Subtest IV of the Token Test for Children assessment was below the normal range. Finally, Murdoch and Hudson-Tennent [38] observed that while the high-level language assessment, the Test of Language Competence (TLC) was attempted, extreme difficulty in understanding the requirements of each subtest resulted in this assessment not being completed. Therefore, in addition to some subtle language disturbances noted by Murdoch and Hudson-Tennent [38], it is unknown whether the difficulties encountered by this child in relation to comprehension of the instructions of the TLC were in fact high-level language disturbances that may have been consistent with the subtle difficulties observed in Case 5 of the current study.

At a group level, performance on an assessment of phonological awareness indicated pre-literacy skills of the brainstem tumour group were within normal limits, despite reports of later literacy difficulties in children with brain trauma diagnosed with acquired aphasia (e.g. [1,13,21]). Even at an individual level, only one isolated impairment was noted in Case 2. Although most of Case 2's scores ranged from falling within the normal range to one standard deviation above the normal range, on the assessment of phonological awareness skills (QUIL), performance on the *Phoneme Detection* subtest was slightly below the normative values. The *Phoneme Detection* subtest targets the ability to listen to the sounds in either the first, end, last, or middle position within each of the four words presented for each item and to determine the odd one out. Reduced performance on this task may, therefore, reflect a specific weakness in this area post brainstem tumour. However, as this reduced score falls just outside of the normal range, and appears particularly uncharacteristic given the performance on the remaining nine subtests, it is also possible that external factors such as fatigue and reduced concentration may explain this performance. In addition, it is important to remember that children who undergo treatment and/or management for a chronic disease such as brain tumour often experience long periods of hospitalization and recovery, as well as often attending many follow-up medical appointments in the period of time subsequent. These factors highlight that schooling can often be interrupted with the potential for the acquisition of specific phonological awareness skills to be impacted. Consequently, factors other than the brain tumour and its management may be influencing performance on this subtest.

Although the present group of children treated for brainstem tumour represent a heterogeneous population, it was interesting to note that in the context of those participants who presented with normal language function, such findings were not consistent with any specific pattern of treatment or duration post treatment. Performance by Case 4 across assessments of language and phonological awareness were noted to be within the normal range, and in some cases above the normal range. Intact language abilities in Case 4, who underwent surgical excision as the only form of treatment for an astrocytoma in the medullopontine angle, may have demonstrated that although later intellectual outcomes specifically related to surgery have been documented by one author [23], late language changes in the case are unlikely given that more than six years has elapsed since treatment.

Case 6 also underwent surgical debulking of an astrocytoma in the lower brainstem. Subsequent chemotherapy was also administered. However, language abilities in this case were again not indicative of any disturbances to this area. Therefore, reports of neurotoxicity, encephalopathies (ranging from subclinical EEG changes and drowsiness to coma and convulsions), encephalomyelopathy, severe neurologic impairment, and mild cerebral dysfunction associated with chemotherapy [2,9,22], among others, were also not seen to impact performance or were evident in either the general or high-level language and phonological awareness abilities in this case.

The effects of treatment for a childhood brain tumour have been well documented and often suggest far-reaching effects, particularly where combinations of treatments have been employed. In the current study, three of the six participants treated for brainstem tumour (Cases 1, 2, and 4) received only one treatment modality, while the remaining three (Cases 3, 5, and 6) were treated with a combination of techniques.

While some participants received either radiotherapy alone (Cases 1 and 2), surgery alone (Case 4), or surgical intervention followed by chemotherapy (Case 6), it is of significance in terms of future research that Cases 3 and Case 5 were the only participants treated for brainstem tumour that underwent a combination of both radiotherapy and chemotherapy. Of these, Case 5 was the only participant to demonstrate any form of language disturbance in the area of high-level language. As Case 3 did not undergo testing for high-level language due to age, it is unknown whether Case 3 would eventually exhibit high-level language disturbances as observed in Case 5. It is noted that the only participant in the study by Murdoch and Hudson-Tennent [38] with a tumour involving the brainstem, was also the only participant to have received a combination of both radiotherapy and chemotherapy.

As outlined, the chemotherapeutic drugs tamoxifen, CCNU, and etoposide were administered to Case 5 over a course of four years, with subsequent radical radiotherapy to the brainstem using posterior oblique fields (total dose of 54 Gy in 30 fractions over six weeks). Treatment approaches utilizing a combination of radiotherapy and chemotherapy have been reported to be associated with significant late effects, including language deficits [28,39]. In fact, the number of treatment modalities employed has been associated with poorer intellectual function and achievement [10,17, 34]. Not only has the toxicity of chemotherapeutic agents been documented to be enhanced by radiotherapy [54], radiation in combination with chemotherapy has also been reported to produce radiation necrosis, parenchymal ischemia and infarction [3,6,22]. In addition, the particular sequence of radiotherapy following chemotherapy as in Case 5, was reported by Silverman and Thomas [48] to be an influencing factor of neuropsychological sequelae following treatment.

The documented treatment effects of the specific chemotherapeutic agents consisting part of Case 5's intensive treatment program administered over a total period of four years include bone marrow suppression, nausea and vomiting, diarrhoea, hair loss, mucositis, hypotension, allergic reactions, infertility and renal, pulmonary, hepatic, and cardiac toxicities [20,22,49, 54]. In particular, the agent etoposide has been associated with known neurotoxicity [20,22,49,54], and was part of a treatment protocol for ten children in which neuropsychological problems were documented in a study by Sands et al. [42]. These children were observed to have overall intelligence difficulties, particularly in the areas of verbal reasoning and abstract visual reasoning. As Case 5 was found to experience difficulty in generating lexical structures in the current study, it is possible that the chemotherapy drugs administered together with radiotherapy may have been a contributing factor influencing function. Case 3 was also administered the chemotherapeutic agent etoposide and was found to have intact general language abilities, as did Case 5. However, as previously highlighted, it is undetermined if Case 3, who did not undergo testing for high-level language, will eventually exhibit disturbances of high-level language similar to Case 5. While considered a limitation for the present analysis, it is highlighted that future research should included further testing of Case 3 at an appropriate age.

A factor that may have also impacted performance in the current study was Case 5's age at the time of treatment, as the impact of treatment on the young child is well documented as being significantly increased compared to older children (e.g. [50]). Chemotherapy was commenced at the age of 20 months through to 4 years of age, at which time radiotherapy was administered. Age related effects are mostly reported in relation to the known effects of radiotherapy, for which the impact is often considered more serious in young children aged under 3 to 4 years, who are considered more susceptible to late neuropsychological damage [41]. Some authors have even documented greater severity of impairment and incidence of abnormal CT scans and neuropsychological evidence in children up to 6 and 8 years of age [22,47]. Therefore, difficulties in high-level language demonstrated particularly by Case 5 may indeed have been at least in part attributable to the combination of both radiotherapy and chemotherapy in the management of brainstem glioma and potential age effects. Again, it is recognized that Case 3 was also under the age of 3 years at diagnosis, and yet as this case was not of appropriate age to undergo high-level language assessments, it is unknown as to whether these higher cognitive areas of language ability would be impacted at a later stage.

Another factor unique to both Cases 3 and 5 was the known presence of hydrocephalus. The indirect effect of hydrocephalus on the brain's structure and function is a recognized cause of language deficits [24–26,35,36]. While Case 5 demonstrated specific areas of reduced high-level language abilities, Case 3's level of function could not be assessed. However, the similar profiles shared by these two cases, despite the younger age of Case 3, may indicate the potential for later difficulties for Case 3.

It must be acknowledged, however, that despite these findings in context of the above factors, Case 5 exhibited a long-term reduction of performance in just two scores over many parameters of both general and high-level language and phonological awareness. Therefore, the influence of performance factors such as fatigue and reduced concentration may have also impacted these results and should not be discounted.

5. Conclusion

Despite some subtle high-level language disturbances evidenced by Case 5 in the area of generating lexical structures, a group analysis of the high-level language abilities of participants treated for brainstem tumour revealed no significant differences when compared to a group of individually matched peers. Similarly, analysis revealed no group differences in phonological awareness, although one participant revealed an area of isolated weakness in a specific area of phonological awareness. Overall, despite predictions of the potential for language dysfunction based on neuroanatomical connections [31], no overt language signs were detected following treatment for brainstem tumour.

While the current data did not reveal the presence of any overt language impairments in children treated for brainstem tumour, it is important to remember that although the current assessment battery was extremely comprehensive and covered more aspects of language than that which had been previously addressed to date [38], such measures are recognized to be basic tests that may also not be sensitive enough to detect subtle language changes. Therefore, it is impossible to rule out the presence of subtle lexical and semantic disturbances that may be identified by more sensitive assessment techniques. However, it is reasonable to suggest from current findings that at a functional level, children treated for brainstem tumour exhibit adequate general language abilities post treatment.

A closer examination of this population is still warranted, however, due to the subtle difficulties that may remain evident in the area of high-level language, as suggested by Case 5's data and the case study reported by Murdoch and Hudson-Tennent [38]. Additionally, further testing of Case 3 (who demonstrated similar characteristics and received similar treatments to Case 5, despite not being of appropriate age to be administered high-level language assessments) would reveal further clarification of the potential of the contributing factors discussed in relation to Case 5. Factors such as combination treatments consisting of both radiotherapy and chemotherapy, as well as young age at time of treatment were suggested to have contributed in the present analysis.

Close monitoring of children treated for brainstem tumour is also considered relevant due to the intensive treatment that is often undergone particularly where combinations of treatment are employed. Such monitoring needs to be ongoing, particularly in children undergoing radiotherapy as part of their treatment, as neuropsychological sequelae often increase concurrently with the amount of time following radiation treatment.

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