Incidence and prognostic factors of ataxia in children with posterior fossa tumours

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Conflict of Interest

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Abstract

Background

There is minimal literature specific to motor outcomes in children with posterior fossa tumours (PFTs) despite ataxia being a significant problem in this group. This study aims to report children’s physical outcomes following management of PFT and determine which factors impact on severity of ataxia and functional limitations.

Methods

42 Children aged between 5-17 and between 1-4 years following surgery for PFT were assessed using The Scale for the Assessment and Rating of Ataxia (SARA), Brief Ataxia Rating Scale (BARS) and the mobility Paediatric Evaluation of Disability Index (PEDI) subscale to determine prevalence and severity of ataxia and a measure of physical function. Analysis was undertaken comparing impact of tumour location, tumour histology, adjuvant treatment, age at diagnosis, presence of pre-operative ataxia and presence of cerebellar mutism syndrome (CMS) on ataxia and physical function scores.

Results

71% of children demonstrated a SARA and BARS score greater than 2. 48% of children had a PEDI scaled score over 90. There was no correlation between age at diagnosis or pre-operative ataxia and assessment scores. There was a significant difference in scores of the SARA/BARS and PEDI depending on tumour histology, tumour location and presence of CMS.

Conclusions

A high proportion of children (>1 year) following surgery for PFT continue to present with ataxia. Higher ataxia and lower physical function scores were demonstrated in children with
medulloblastoma, midline tumours and those diagnosed with CMS. The high prevalence of ataxia demonstrates the need for further research regarding rehabilitation management in this population.

Key Words; Posterior fossa tumour, ataxia, paediatrics

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Introduction

Brain tumours are the most common type of solid tumour diagnosed in children, and approximately 50% of all childhood brain tumours are location in the posterior fossa region. Management of posterior fossa tumours (PFTs) typically involves surgical resection; solely or in combination with adjuvant treatments such as radiotherapy and chemotherapy. The potential for gross change peri-operatively is documented, but detailed motor outcomes and predictors of short and long-term outcomes remain relatively ill defined.

Ataxia describes the predominant and most disabling collective of motor clinical signs in children with PFTs before and following intervention. Indeed 58-90% of children with PFTs present with this sign, frequently describing either balance or gait impairment, tremor, speech disturbance or incoordination. Balance and co-ordination problems can affect activities of daily life, return to school and participation with peers and therefore it is important to gain further insight into these problems.

Ataxia often persists post-operatively, but current literature focuses on neuropsychological and cognitive long-term outcomes. Ataxia is less well described despite its reported high prevalence. Recent research by Piscione et al (2014) reported 70% of children with PFTs have long-term post-operative balance problems, alluding to ataxia, but it remains unclear as to what prognostic factors, if any, exist peri-operatively to determine this risk of outcome. An exploration of prognostic factors for impairment and functional limitations following management of PFT is further made challenging when set against normal childhood development. However, understanding the long-term impairment and functional limitations of children with PFTs by identifying and quantifying potential
prognostic factors, remains necessary to inform overall management and tailor rehabilitation packages.

To date there is minimal evidence to guide the type, intensity and timing of physiotherapy intervention for children with ataxia. Literature on physiotherapy for people with ataxia has focused on the adult population with a suggestion of benefit from conventional physiotherapy, treadmill training and video-gaming. However, it is not clear if these interventions will have the same impact in children with ataxia following management of posterior fossa tumours. Gaining an understanding of prognostic factors may help design physiotherapy programmes and guide future research.

This study provides a new insight pertinent to the management of PFT by quantifying motor outcomes for children (aged 5-17 years) between 1 and 4 years following surgical resection and any adjuvant oncological treatment. It presents novel data based on recently validated standardised measures of ataxia and motor-related function for both children and adults, namely incorporating the Scale for Assessment and Rating of Ataxia (SARA), the Brief Ataxia Rating Scale (BARS) and the Pediatric Evaluation of Disability Index (PEDI). It explores potential prognostic factors for long-term outcomes such as age, overall management (adjuvant treatments; radiotherapy and chemotherapy) as well as tumour histology and location.

Materials and Methods

Design

This prospective cross-sectional study was approved by the Liverpool East Research Ethics Committee and local R & D office.

Participants

Children with a posterior fossa tumour who had surgical resection of a posterior fossa tumour undertaken between 1 to 4 years earlier, and who were aged between 4 and 18 were eligible for
inclusion. Those who were within a year of resection or still undergoing chemotherapy or radiotherapy were excluded. Children were recruited from a single Tertiary Neurosurgical/Oncology Unit in the UK between 2012 and 2016.

**Procedures**

Potential participants were identified and screened for eligibility using a database of children with brain tumours treated at Alder Hey Children’s NHS Foundation Trust, Liverpool, England. Informed and written consent was obtained from all children and/or their parents (with child assent) and data managed in accordance with the Declaration of Helsinki (2004).

Children who entered the study were assessed by a neuro-paediatric physiotherapist (from a team of 3 therapists) whilst attending the tertiary centre for a clinic follow-up visit. The raters underwent a joint training session in order to optimise inter-rater reliability of outcome measure collection prior to commencement of the study.

**Ataxia outcome measures** were objectively assessed by one of 3 physiotherapists known to the child. These include the Scale for the Assessment and Rating of Ataxia (SARA) (the SARA can be found in the appendix supplementary data of the original validation study by Schmitz-Hubsch et al 2006)\(^1\), the Brief Ataxia Rating Scale (BARS) (the BARS can be found in the original validation study by Schmahmann et al 2009)\(^2\) and a Global Clinical Impression (GCI)\(^3\) of ataxia severity (categorized as: no; mild; moderate; or severe). The mobility domain of the Pediatric Evaluation of Disability Index (PEDI) was used as a functional mobility outcome measure (the PEDI can be found in the original PEDI manual by Hayley et al 1992)\(^4\). Order of completion of rating scales was randomized to minimize fatigue and practice effects.

**Baseline disease descriptors** collected from pre-existing research database entries, including tumour histology, age at diagnosis and assessment, presence of pre-operative ataxia (recorded as yes or no), adjuvant treatment (radiotherapy or chemotherapy), paediatric neurosurgeon who completed the surgical resection, and recording of cerebellar mutism syndrome (CMS), were compared against physiotherapy outcome measures.
All pre-operative imaging from children who were assessed was independently (blindly) reviewed (without reference to any assessment findings) by a consultant paediatric neurologist and tumour location was classified as either midline or non-midline.

**Measures**

The Scale for the Assessment and Rating of Ataxia (SARA) and the Brief Ataxia Rating Scale (BARS) are valid, reliable standardised measures of ataxia, commonly cited in research and used clinically. The SARA has eight items and has a total score out of 40, a higher score indicating more severe ataxia. The BARS has five items and is scored out of 30, again a higher score indicates more severe ataxia. They demonstrate high inter-rater reliability in both adults and children and hold a significant correlation with the more traditionally used rating of ataxia, the International Co-operative Ataxia Rating Scale (ICARS), whilst taking a much shorter time to complete. There is also emerging reports of good correlation (SARA r= -0.77, BARS r= -0.76) between the scales and the mobility domain of the PEDI (Paediatric Evaluation of Disability Index) for children with PFTs.

The Paediatric Evaluation of Disability Index (PEDI) is a valid and reliable functional measure in paediatric acquired brain injury. It has self-care, mobility, and social function sections, which are used as whole or stand-alone domains. It is completed by parental questioning or examination from the therapist. Only the mobility domain of the scale was collected, termed PEDI-m, to minimise time-related burden on participants compared with the ‘complete PEDI’ recommended 45-90 minute assessment.

**Data analysis**

Descriptive statistics were utilised to describe the prevalence of ataxia and functional motor deficits. Clinical outcome variables (SARA, BARS and PEDI-m) were not normally distributed (Kolmogorov-Smirnoff test <0.005) and therefore data was analysed and presented according to non-parametric methods in SPSS (IBM v.22, New York, USA). The PEDI is normative referenced between 6 months and 7.5 years. In line with recommendations, raw scores were converted to scaled scores to enable the
use of the PEDI-m in children over the age of 7.5 years. PEDI scaled scores range from 0-100 with a higher score representing a better level of physical function.

Spearman’s rank correlation coefficients explored associations between the core motor outcome measures (the SARA, BARS and PEDI-m) and age at diagnosis. The Mann-Whitney U test explored hypotheses that tumour histology, adjuvant treatment, neurosurgeon experience, presence of pre-operative ataxia and tumour location could affect the core outcome measures. In all cases alpha was set at 0.05, with a corresponding significance level of 5%. Subgroup analysis was undertaken using the Mann-Whitney U test (significance level 5%), in order to explore the impact of variables such as tumour location, tumour histology and intervention modalities after PFT resection.

**Results**

**Study Sample**

Eighty-six patients were screened for eligibility, 76 of which were approached (10 excluded due to age), of which 72 consented, as illustrated in Figure 1. From this patient group 42 patients completed the standardized assessments between 1-4 years post-surgical resection and were thus eligible for analysis for this part of the study. Twenty (48%) were male, with the age range of children between 5 and 17 years. 57% were receiving physiotherapy at the time of assessment. Sample characteristics are detailed in Table 1.

**Ataxia Outcome measures**

**Scale for assessment and rating of ataxia**

The median SARA score is 4.25 (range 0-29). A higher score (maximum 40) represents more severe ataxia. (See supplementary Table 1 for raw scores).

**Brief Ataxia Rating Scale**

The BARS scores range from 0-24 with a median of 4.0, again a higher score (maximum 30) referring to a higher degree of ataxia. (See supplementary Table 2 for raw scores).
From previous work (with children over the age of 7) it was suggested that a score of 2 in either the SARA or the BARS can be used as a threshold for distinguishing no ataxia from mild ataxia\(^1\). On this basis 30 (71\%) of the children assessed are classified as having ataxia.

**Ataxia global impression scale**

Clinical Global Impression scale scores report that 12 (29\%) have no ataxia, 17 (40\%) have mild ataxia, 7 (17\%) have moderate ataxia and 6 (14\%) have severe ataxia.

**Paediatric Evaluation of Disability Index: Mobility score (PEDI-m)**

The median scaled PEDI-m score is 85.2 (range 30.6 to 100; maximum score 100). Fourteen children demonstrate a scaled score of 100 (high functional capability), with a further 20 children (48\%) scoring over 90. Three children demonstrate scores ranging between 54.8 and 85.2. Five demonstrate lower functional mobility capability with scaled scores of below 50.

**Exploring baseline disease descriptors as predictors of post-operative clinical score change**

Several variables were analysed to identify their possible impacts on ataxia and motor outcomes (namely the SARA, BARS or PEDI-m scores). Given the ordinal nature of the scales, all comparisons were explored using non-parametric methods.

**Age at diagnosis:** There are no correlations between age at diagnosis and SARA, BARS or PEDI-m score (SARA -0.24, BARS -0.12, PEDI 0.25 respectively).

**Tumour histology:** Due to small numbers of ependymoma (n=5) and CP angle schwannoma (n=3), only the medulloblastoma (n=13) and low-grade glioma (n=21) remain suitable as comparators within hypothesis testing. A significant effect of tumour histology is reported in scores of the SARA, BARS and PEDI-m score (p<0.001, p=0.001, p=0.004, respectively). *Medulloblastoma* group median SARA and BARS ataxia scores are higher than those of the *low-grade glioma* group (9.5 and 9 compared with 2.5 and 2 respectively) and PEDI-m score lower (50 compared with 58), suggesting that children with medulloblastoma typically feature more severe ataxia and lower functional motor ability.
**Tumour location**: Significant differences are also reported in median SARA, BARS and PEDI-m scores according to grouping by tumour location (p<0.001, p=0.007, p=0.01, respectively). The SARA and BARS scores were higher and PEDI-m scores lower in the midline (m) group compared with non-midline (nm) group ([SARA: m=6.5, nm=1.5], [BARS: m=5, nm=1], [PEDI-m: m=54, nm=59]), suggesting that this midline zone was associated with severe ataxia and lower functional motor ability.

*Low grade gliomas* do feature mixed locations in terms of midline and unilateral histology. Subgroup analysis of those with low grade glioma was therefore additionally examined for trends within core outcome measures depending on tumour location. This data (Table 2) reveals a trend for those with low grade gliomas and midline tumours to have notably higher SARA/BARS scores and lower PEDI-m scores. However, due to low numbers there is not enough power within this analysis to report a statistically significant difference in scores.

*Pre-operative ataxia*: There is no difference in SARA, BARS and PEDI-m scores in children who were reported to have pre-operative ataxia compared to those who were reported to have no ataxia pre-operatively (SARA 0.16, BARS 0.16, PEDI 0.13 respectively).

Surgical experience: Data was available for 40 children. An individual consultant paediatric neurosurgeon operated on 25 of the children in this study, the remaining 15 children were operated on by a range of 8 neurosurgeons. Due to the variation in number of operations completed by the paediatric neurosurgeons and an unknown quantification of operations undertaken by all concerned (historically and outside the institution in question), the only suitable comparator of experience was between two groups; an individual frequent PTF operator consultant paediatric neurosurgeon (‘individual’, n=25) compared with the group of 8 less frequent group PTF operators (‘group’, n=15). There is no difference between the individual and group SARA, BARS and PEDI-m scores, (SARA median 3 and 4 respectively, BARS median 4 and 3 respectively, PEDI scaled score 94.2 and 85.2 respectively). The study was not powered to detect a difference using statistical analysis.
Cerebellar mutism syndrome: There is a significant difference in SARA, BARS and PEDI-m scores in children who were reported to have CMS post operatively compared to those reported without CMS as illustrated in Table 3. The SARA/BARS scores were both higher and PEDI-m score lower in the CMS group, suggesting that CMS post-operatively is associated with more severe ataxia scores and lower functional motor ability.

Adjuvant treatment: Table 4 reports SARA, BARS and PEDI-m scores for children assessed with respect to the oncological treatment they received. Children who underwent surgery, radiotherapy (RT) and chemotherapy notably demonstrate higher ataxia scores and lower PEDI scores than both children who underwent surgery and RT or those who had surgical treatment alone. Due to the small number of children in the surgery and radiotherapy group, these findings are best reported as trends and statistical hypothesis testing between the three groups was not undertaken. It is at this point also worth acknowledging that children undergoing RT and chemotherapy will have received differing dose/frequency of RT and differing chemotherapy regimens dependent on individual protocols, representing significant variation in adjuvant treatment.

Discussion

This is the largest study to date quantifying ataxia and physical functioning in children following management of a posterior fossa tumour. The results highlight that a considerable proportion of children will continue to present with long term ataxia and functional mobility problems (between 1 – 4 years post-surgical resection). The results in this study indicate that 71% of children present with ataxia after one year, which is comparable to 70% of children with balance problems reported by Piscione et al (2014). Sonderkaer et al (2003) further report that 68% of children have ataxia at the point of presentation, which could imply that ataxia is a direct consequence of PFT histology rather than a consequence of subsequent management.

The results of this study also support prior reports of children continuing to present with neurological sequelae (although not specifically physical function) years following treatment in almost 50% of
samples studied\textsuperscript{3,20}. Encouragingly, most of the children feature ataxia at the milder end of the spectrum and still retain a high mobility capability. However, despite mild classification of ataxia and mild mobility restrictions, the presence of any ataxia signs could still precipitate disability and participation restrictions for children, worthy of future research in this area. This is supported by twenty four (57\%) of the children continuing to receive physiotherapy input at the time of their assessment.

There was no association between ataxia and mobility scores and age of children at diagnosis. This is in agreement with other studies that reported no influence of age at diagnosis\textsuperscript{7,20}. However, there are a small number of studies that report being diagnosed at a younger age results in greater disability\textsuperscript{22,23,24}. This is potentially owing to an under-developed sensory motor system being affected compared with that of an optimised system in adult age. Additional research in this field appears to be indicated in view of the conflicting findings and varying methods within studies (predominantly employing retrospective questioning of adult survivors many years after PFT management).

There was no significant difference found in scores for both ataxia rating scales and the PEDI-m dependent on presence of pre-operative ataxia. However, it should be noted that presence of pre-op ataxia was recorded only as present or not, from pre-existing data available. Ataxia was noted as a presenting sign in 22 children (55\%, data not known for two participants) which is in line with other reports\textsuperscript{2,25}. Formal pre-operative assessments were not completed as part of this study, though the use of ataxia scale assessments pre-operatively would add value to longitudinal studies to allow direct comparison pre-post operatively and this should be considered for future research.

There was no difference in scores for both ataxia rating scales and the PEDI-m dependent on the paediatric neurosurgeon who completed the surgical resection. Although it was noted that there was not an even split in neurosurgeons for analysis (one consultant paediatric neurosurgeon frequently operating on PFT compared with a group of 8 less frequently PFT operating neurosurgeons). Previous literature has reported that extent of tumour resection (and mortality)\textsuperscript{26,27} can be influenced by surgical experience although the impact on any subsequent neurological deficit
is less clear and could be examined further in larger studies. Before this can be investigated further a method of quantifying experience of surgeons needs establishing and sample size estimations undertaken to inform adequate powering of future research.

There was a significant difference found in scores for both ataxia rating scales and the PEDI dependent on tumour location (midline versus unilateral) and tumour histology. This effect of tumour histology is consistent with past reports that children with medulloblastoma present with more balance and fine motor problems and poorer health related quality of life. Subgroup analysis in this study, examining influence of location in children with low grade gliomas, indicated that midline location may be a risk factor for more severe ataxia within this histological group. This in turn could suggest that tumour location rather than specific histological tumour type may be more of a predictive factor. The increasing depth of literature on cerebellar mutism syndrome (CMS) suggests specific tumour infiltration of the brainstem and fourth ventricle location are the only consistently reported risk factors of CMS again highlighting the importance of specific location. Despite best attempts, it remains difficult to isolate the impact of single variables (histology, location, resection procedure, radiotherapy or chemotherapy) on the ataxia and mobility in children with PFTs, given the potential for these variables to interact. Children with medulloblastoma, due to the nature of the tumour type, typically feature midline tumours and receive multi-modality therapy i.e. radiotherapy and chemotherapy. This study also only had scope to consider a limited classification of location of PFT (midline or unilateral) and would benefit further if pathological changes to more precisely reported structures could be explored. Literature reporting ataxia in both the genetic population and in children with post fossa tumours considers involvement of the deep cerebellar nuclei a key factor in persistent ataxia reiterating the importance of tumour location. Exploration of long term ataxia and mobility restrictions alongside knowledge of primary or secondary histological changes to the nuclei, cerebellar peduncles, vermis or hemispheres, for example, could potentially improve future prognostic abilities.

In this study, 9 children were reported to have CMS in the initial post-operative period. The tumour histology was mixed (3 low grade glioma, 5 medulloblastoma, 1 ependymoma) and eight out
of nine were classified as midline. Despite the small sample size, there is a trend in this group towards increased long term ataxia and functional mobility problems, similar to other literature that report increased long term neurocognitive and speech problems in children diagnosed with CMS post operatively. There is emerging literature regarding the potential to predict the risk of CMS and this strategy should be explored alongside specific reference to ataxia to minimise the risk of neurological deficit as a result of cerebellar pathology.

Consistent with prior research reports, a trend in this study’s data points towards higher ataxia scores in children who have received radiotherapy and chemotherapy as adjuvant treatment. Although inherently linked with tumour histology and location as discussed above, Piscione et al 2014 suggest that receipt of chemotherapy can contribute to predicting motor function, via mechanisms such as chemotherapy toxicity impacting on physical functioning. It is reported that children who undergo chemotherapy can present with long term motor and sensory problems secondary to chemotherapy toxicity that can affect physical function. In particular the neurotoxicity of chemotherapy agents such as vincristine are acknowledged, although all but one participant who received chemotherapy had vincristine as part of their treatment protocol therefore potential effects of this were not possible to be reviewed in isolation. Chemotherapy induced neuropathy was not explored in this study and it must be acknowledged that some children (notably those assessed at 1-year post surgery) who may still be in recovery from adjuvant treatment could have featured this at the time of assessment.

This study is one of few to use standardized ataxia and validated paediatric functional outcome measures to enable clear and objective reporting of clinical assessment findings. It is noted that there is increased variability in scoring reported when using the ataxia scales in children under the age of 8. However, only 4 children in this participant group were under this age threshold and there remains no alternative co-ordination assessment tools in this younger group, thereby justifying their use in the case of this study. The PEDI was chosen as it is validated in the acquired brain injury population and can be used in children over the age of 7, but is only normative referenced up to this
Scores were converted to scaled scores to account for this, but it is acknowledged that using a tool with wider normative referencing would have added benefit to this study. One of the few studies to also look at physical functioning in children with brain tumours by Piscione et al 2014 used the BOT-2 (Bruiniks-Osteretsky Test of Motor Performance second edition), which had the advantage of being normative referenced from 4-21 years. However, although it has been evaluated in children with developmental coordination disorder, it is not validated in children with acquired neurological problems and therefore not selected for use in this study. It would be of interest to evaluate the psychometric properties of the BOT-2 in children with brain tumours, and potentially compare its use with the scales used in this study as it could examine coordination, balance, running speed and strength to provide a broader construct of motor performance compared with that of the PEDI.

Although this study has a fairly large sample in relation to literature in this area, with assessments completed within a defined time frame of 1-4 years post-surgery, it is acknowledged that to allow the results to be generalised to the larger paediatric posterior fossa brain tumour population a still larger sample would be required. This would further enable a fully powered sub group analysis, as at present there are small numbers in some groups e.g. children with ependymoma. Future larger studies with validated motor outcome measures, possibly attached to national and international treatment trials, are advocated in order to confirm these findings and further the understanding of complex interactions between histology, tumour location and multimodal therapies. This study demonstrated that tumour histology and tumour location are predictive of severity of ataxia and physical function. A larger study could allow comparison between standardised groups which included different adjuvant treatment regimes to allow further analysis of which factors have the most impact on motor problems.

**Conclusion**

This study provides a new contribution to knowledge of ataxia and physical function following posterior fossa resection in children. Overall ataxia was reported in a significant proportion of the children with an associated impact on functional mobility. These issues were more prevalent in
children with medulloblastoma and midline tumours. This new knowledge may be valuable to therapists and families when planning post-operative rehabilitation programmes as well as helping to inform the design of clinical trials. This study demonstrates that the chosen ataxia measures if reliably applied could be used in future trials/audits of service outcomes as a measure of quality of survival.

Future research would be of value to prospectively longitudinally assess children following PFT resection at specific time points. A natural history of ataxia and functional change in this population may provide information as to when to maximise therapy. Whilst observational research continues, there is also a need to pragmatically explore the impact of therapy in this patient group to determine whether contemporary rehabilitation programmes can produce improved outcomes.

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Conflict of Interest

H Hartley, Prof Pizer, Dr Lane, C Sneade, R Williams, Mr Mallucci, Dr L Bunn, Dr Kumar all report no conflict of interests.

Captions

Tables

Table 1. Baseline Characteristics of participants (n=42)

Table 2. Subgroup analysis in children with low grade gliomas
Table 3. Analysis of scores in relation to CMS

Table 4. Analysis of scores in relation to treatment type

**Figures**

Figure 1. Participants (STROBE Flow Diagram)

**References**


