Long-term quality of life in children treated for posterior fossa brain tumors

Clinical article

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Object. In the face of increasing survival, quality of life (QOL) has become an important indicator of treatment success in children with posterior fossa brain tumors (PFBTs). The authors’ objective was to assess the long-term QOL in survivors of PFBT.

Methods. The authors conducted a cross-sectional study of children who, between birth and age 18 years at diagnosis, had previously been treated at their institution for a PFBT. At the time of assessment for this study, children were between 5 and 19 years old and had received standard treatment for PFBT ending at least 6 months before the assessment. The QOL was measured with the Pediatric Quality of Life Inventory (PedsQL) generic score scales and the Health Utilities Index Mark 3 (HUI3). Multivariate analyses were used to assess several variables (patient related, treatment related, and socioeconomic) for association with QOL.

Results. A total of 62 children participated in the study (median age at assessment 11.9 years, interquartile range [IQR] 7.8–14.8, and median age at tumor diagnosis of 4.9 years, IQR 2.5–6.9). Median time since active treatment for their PFBT was 5.2 years (IQR 2.4–10.1). Tumor types included cerebellar pilocytic astrocytoma (45.2%), medulloblastoma (30.6%), ependymoma (11.3%), and brainstem astrocytoma (11.3%). Adjuvant therapy included chemotherapy (40.3%) or radiotherapy (14.5% focal and 21.0% craniospinal radiotherapy). Permanent treatment for hydrocephalus was required in 38.7% of the patients. Tumors recurred in 11.3%, requiring repeat treatment in these patients. The median HUI3 utility score was 0.91 (IQR 0.71–1.00) and the median PedsQL total score was 78.3 (IQR 64.1–92.4). Only the following variables were significantly associated with decreased QOL in multivariable model testing (all p < 0.05): need for permanent hydrocephalus treatment, large ventricle size, decreased family functioning, and lower family income.

Conclusions. As a group, long-term survivors of pediatric PFBT appear to have QOL indicators that are similar to those of the general population, although a reasonable minority of patients experience poor outcomes. Although several confounding variables likely remain in this retrospective study, important associations with QOL include the presence of hydrocephalus and socioeconomic factors. The study sample size, however, was limited and the presence of other important factors cannot be excluded.

Object. With better therapies, survival outcomes of PFBTs have improved. It is now recognized that the goals of treatment should include not just survival but QOL as well. The literature on long-term QOL for children treated for PFBT is somewhat limited but has highlighted the difficulties these children can experience in terms of cognitive, physical, social, and psychological outcomes. The objectives of this study were to describe the long-term QOL of children with PFBT treated at Hospital for Sick Children, Toronto, and to identify predictors of QOL.

Methods

This study was approved by the Research Ethics Board of the Hospital for Sick Children. Potential participants were identified by searching a prospectively maintained database of all children with brain tumors treated...
at our institution. We included patients who met the following criteria: 1) Diagnosis of a PFBT of any type, between birth and age 18 years, in patients who required surgery at least 1 year before the QOL assessment. 2) No chemotherapy or radiation therapy received within the last 6 months. 3) No evidence of progressive disease at the time of the assessment. 4) Aged 5 to under 19 years old at the time of the assessment. The outcome measures used in this study are only for those children 5 years or older and the concept of true QOL has been best studied in children who are at least of school age. 5) Parent or primary caregiver was able and willing to provide consent and able to read and write in English, since some of the outcome measures used in the study were only available in English.

Data Collection

Once consent was provided, we collected the following data. 1) Patient-related variables were extracted from the medical chart and included the following: age at assessment, age at first surgery, time since first tumor surgery (years), and time elapsed since last active treatment (chemotherapy or radiation) of tumors (years). 2) Treatment-related variables were extracted from the medical chart and included the following: length of initial hospitalization for PFBT treatment (days), tumor type (cerebellar pilocytic astrocytoma, medulloblastoma, ependymoma, brainstem astrocytoma, or other), postoperative mutism (yes/no), history of tumor recurrence (yes/no), use of chemotherapy (yes/no), use of craniospinal radiation therapy (yes/no), use of any radiation therapy (yes/no), need for permanent hydrocephalus treatment (yes/no), and preoperative and current ventricle size (using the validated frontal-occipital horn ratio, 22,27). 3) Socioeconomic data were determined by self-completed questionnaires given to the child’s parents and included annual family income exceeding $80,000 (which is roughly the median income of all families in Canada: http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/famil21a-eng.htm, accessed October 1, 2012) and whether either parent was a university graduate. The parents were also asked to complete the General Functioning Scale of the McMaster Family Assessment Device or the GF-FAD. 4,23 This scale has proven reliability and validity and is based on a multidimensional model of family functioning that incorporates problem solving, communication, roles, affective responses, affective involvement, and behavior control. The scores on the GF-FAD range from 1 to 4, with an increase in the score indicating increased family pathology.

Outcome Measures

The current QOL of the patients was measured using the following outcome measures.

PedsQL Generic Core Scales. The PedsQL is a 23-item questionnaire that can be completed by the caregivers or by older children. 37,38 It is a generic QOL measure that has been used in many different types of childhood illnesses, including brain tumors. 39 It has demonstrated good reliability and validity in different clinical settings. 35,36 Each of the 23 items describes a specific problem, and the respondent is asked to rate this problem for the child on a 5-point scale (ranging from “never a problem” to “almost always a problem”). The responses are summarized to provide a total scale score (based on all 23 items) as well as separate physical health (8 items) and psychosocial health (15 items) summary scores, along with subscores of emotional, social, and school functioning (5 items each). The scores ranged from 0 (worst outcome) to 100 (best outcome). All caregivers completed the PedsQL, and children over 8 years of age with sufficient cognitive capacity also self-completed a PedsQL questionnaire.

HUI3. The HUI3 is a simple questionnaire that has taken various modified forms and has been used in different pediatric populations including those with brain tumors, and good reliability and validity have been demonstrated. 3,13,26,34 The HUI3 assesses functioning in 7 domains (vision, hearing, dexterity, ambulation speech, emotion, cognition, and pain) and translates the individual health state into a utility score. 12 A utility score is an estimate of the relative preference for that state of health. For example, the utility score for “dead” is 0 and for “perfect health” is 1, and utility scores less than 0 indicate states described as “worse than dead.”

Statistical Analysis

Univariate analysis was used to determine an association between all potential predictor variables and the parent-completed PedsQL total scale score (primary-dependent variable). Continuous variables were tested with univariate regression and categorical variables with t-test or ANOVA. Those variables that appeared to be important (with a p value < 0.1) were entered together into a multivariate generalized linear model regression. This process was repeated using the PedsQL physical health score, the PedsQL psychosocial health score, and the HUI3 utility score as the dependent variable. Only the PedsQL parent-completed responses were used for analyses since the number of child-completed responses was too small. Our analyses were viewed as exploratory, and any variable with p < 0.05 in the multivariable model was considered to have an association of interest with the dependent variable. Analyses were performed using SPSS 17.0 statistical software (SPSS Inc.).

Results

Of 187 potentially eligible patients followed up at the Hospital for Sick Children, 90 (48%) were contacted, of whom a total of 62 (33%) participated between January 2007 and January 2010. Thirty-seven percent of all potentially eligible patients with medulloblastoma participated, 54% of those with ependymomas, 31% of those with cerebellar astrocytomas, and 30% of those with brainstem astrocytomas. The baseline characteristics, treatment-related factors, and socioeconomic characteristics of these patients are shown in Table 1. Thirty-one children (50%) were younger than 5 years at tumor diagnosis and 10 (16.1%) were younger than 2 years old.

The QOL outcomes for the cohort are shown in Table
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2. The mean parent-completed PedsQL total scale score and HUI3 utility score for the different tumor types were the following, respectively: pilocytic astrocytoma (79.5 and 0.80), medulloblastoma (72.7 and 0.80), ependymoma (80.3 and 0.98), and brainstem astrocytoma (79.5 and 0.90). The differences in QOL outcome among the different tumor types were not statistically significant (all p > 0.3).

**Regression Analyses**

All variables listed in Table 1 were tested in univariate analyses for an association with the parent-completed PedsQL total scale score. Only the following variables were found to have a p < 0.1 in univariate analysis: preoperative ventricle size, current ventricle size, need for permanent hydrocephalus treatment, and family income greater than $80,000. These were entered into a multivariate model, the results of which are shown in Table 3. Only family income greater than $80,000 (p = 0.007) and smaller current ventricle size (p = 0.013) were associated with a higher PedsQL total scale score. Results of the multivariate models for the PedsQL physical scale score, PedsQL psychosocial scale score, and HUI3 are shown in Tables 4 and 6. The following were associated with a higher PedsQL psychosocial scale score: smaller current ventricle size (p = 0.01), better family functioning (assessed with the G-FAD; p = 0.01), and family income greater than $80,000 (p = 0.03) (Table 5).

**Discussion**

Posterior fossa brain tumors are the most common brain tumors in children. The QOL issues for survivors of pediatric PFBT are unique and relate to many potentially important factors, including physical, intellectual, and psychological concerns. Following surgical excision of a PFBT or as a result of the tumor growth itself, a child may be left with numerous physical deficits, including difficulty walking and running, balance and coordination problems, weakness, difficulty swallowing food, and visual and speech problems. As shown by Aarsen et al., even after treatment of a benign tumor, such as pilocytic astrocytoma, long-standing deficits such as apraxia, motor neglect, and speech dysarthria may persist.1 The impact of any one of these deficits on the QOL of PFBT patients can be significant. Numerous studies have also highlighted the impact of chemotherapy and radiotherapy, especially cranial radiation, on long-term cognitive outcome in children.2,6,14,15,29 These treatments especially...
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TABLE 4: Multivariate analyses of the PedsQL physical scale score

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter Estimate (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>permanent hydrocephalus treatment</td>
<td>−14.0 (−26.7 to −1.3)</td>
<td>0.03</td>
</tr>
<tr>
<td>preop ventricle size, FOR</td>
<td>−4.7 (−10.6 to 1.1)</td>
<td>0.11</td>
</tr>
<tr>
<td>length of hospital admission for initial tumor op</td>
<td>−0.7 (−3.2 to 1.8)</td>
<td>0.55</td>
</tr>
<tr>
<td>cerebellar mutism</td>
<td>−4.5 (−25.4 to 16.4)</td>
<td>0.66</td>
</tr>
<tr>
<td>age at assessment</td>
<td>0.3 (−1.4 to 1.9)</td>
<td>0.75</td>
</tr>
<tr>
<td>age at diagnosis of PFBT</td>
<td>−0.2 (−2.1 to 1.8)</td>
<td>0.86</td>
</tr>
</tbody>
</table>

TABLE 5: Multivariate analyses of the PedsQL psychosocial scale score

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter Estimate (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>current ventricle size, FOR</td>
<td>−220 (−385 to −54)</td>
<td>0.01</td>
</tr>
<tr>
<td>Family Assessment Device</td>
<td>−15.5 (−27.0 to −3.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>annual family income &gt;$80,000</td>
<td>11.5 (1.3−21.7)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

TABLE 6: Multivariate analyses of the HUI-3 utility score

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter Estimate (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>permanent hydrocephalus treatment</td>
<td>−0.2 (−0.4 to −0.1)</td>
<td>0.008</td>
</tr>
<tr>
<td>preop ventricle size, FOR</td>
<td>0.5 (−0.4 to 1.4)</td>
<td>0.290</td>
</tr>
<tr>
<td>tumor recurrence</td>
<td>0.1 (−0.1 to 0.4)</td>
<td>0.290</td>
</tr>
<tr>
<td>Family Assessment Device</td>
<td>−0.1 (−0.2 to 0.1)</td>
<td>0.410</td>
</tr>
</tbody>
</table>
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it is not clear whether there is a true causal relationship between family functioning and QOL and, if so, in what direction. For example, it is possible that family functioning worsens secondarily because of a child who has suffered a poor QOL outcome. Similarly, if a child has had a poor outcome, this might force one or both parents to alter their employment status, resulting in a lower family income.

Our study has important limitations. Our sample size, although one of the largest reported in a QOL study of PFBT, still limited the statistical power of our analyses, and so it is certainly possible that other important predictor variables were not identified in our study. Therefore, we cannot conclude that factors such as tumor type, radiation, and chemotherapy, for example, do not influence QOL. It is quite possible that these variables were false negatives resulting from the limited statistical power. Given its retrospective nature, much of the data collection relied on review of medical records, which will result in some degree of inaccuracy. For example, we found convincing evidence of cerebellar mutism in only 6.5% of our sample. This is almost certainly a gross underestimate of its true prevalence and a reflection of the limitations of retrospective data abstraction. Although our participation rate was reasonably high (69%), it is possible that those families who refused to participate had some characteristics that were systematically different from those of the study participants. If so, our results might not be truly representative of the overall outcome of all survivors of pediatric PFBT. In addition, by selecting only for the long-term survivors, we had biased our sample to those children who have done the very best following the treatment of their PFBT.

Conclusions

As a group, long-term survivors of pediatric PFBT appear to have QOL indicator scores that are similar to those of the general population, although a minority of these survivors experience poor outcomes. Although several confounding variables likely remain in this retrospective study, important associations with QOL include the presence of hydrocephalus and socioeconomic factors.

Disclosure

This study was funded by a grant from b.r.a.i.n.child. The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: all authors. Acquisition of data: Kulkarni, Piscione, Shams. Analysis and interpretation of data: Kulkarni, Piscione, Bouffet. Drafting the article: Kulkarni. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Kulkarni. Statistical analysis: Kulkarni. Administrative/technical/material support: Kulkarni, Shams. Study supervision: Kulkarni.

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