Prevalence, associations, and predictors of apathy in adult survivors of infantile (<5 years of age) posterior fossa brain tumors†

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Background. Apathy is associated with pervasive and disadvantageous effects on daily functioning. It has been observed transiently in some children after surgery for posterior fossa tumors. In this study, our objective was to examine prevalence, associations, and predictors of apathy in adult survivors of an infantile posterior fossa brain tumor (PFT).

Methods. One hundred seventeen adult survivors of a childhood PFT diagnosed before age 5 years and 60 of their siblings were assessed in a cross-sectional study a mean of 32 years (range, 18–53 years) after survivors’ initial tumor diagnoses, using the Marin Apathy Evaluation Scale (AES), the Weschler Abbreviated Scale of Intelligence and the Composite International Diagnostic Interview for psychiatric disorders.

Results. Marin Apathy Evaluation Scale, the Weschler Abbreviated Scale of Intelligence reached or exceeded a criterion score for clinically significant apathy in 35% of survivors, compared with 18% in a sibling comparison group. In both siblings and survivors, apathy was associated with lower verbal and full-scale IQ and, among survivors, with having undergone partial rather than total tumor resection (independent of irradiation status). Apathy was not related to presence of concurrent International Classification of Diseases, 10th Revision, depression. Female sex was associated with late apathy after a PFT, with increased likelihood of women reaching the apathy criterion relative to men if they were survivors.

Conclusions. Clinically significant and potentially treatable apathy occurs relatively commonly in adult survivors of an infantile childhood PFT, particularly women. Clinicians, including those managing posterior fossa pathology in very young children, should be aware of this association, and future research should clarify whether specific treatment-related variables are implicated in increasing this risk of apathy.

Keywords: apathy, cancer, cerebellum, cognitive, infancy, radiotherapy, survivorship.

In the context of improving survival rates after treatment of childhood cancers, there is increasing interest in the later quality of survivorship—an area of study that was previously relatively neglected.1,2 Consideration of long-term outcomes after brain tumors in the youngest infants is particularly relevant because of the increasing numbers of survivors of increasingly aggressive pediatric brain tumor treatment protocols.3,4 In a wider project examining long-term neuropsychiatric outcomes after treatment for a posterior fossa brain tumor (PFT) in early childhood, we

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assessed the presence of apathy in a group of adult survivors who had received a diagnosis of a PFT before 5 years of age.

Apathy is a disorder of diminished motivation defined as a deficiency in behavioral, emotional, and cognitive components of goal-directed behavior. Its presence may be associated with a range of pervasive and disadvantageous effects on daily functioning. It occurs in several conditions of acquired brain damage, including Parkinson's disease, stroke, dementias, and traumatic brain injury. Of particular relevance to the current study, apathy has been reported in association with single cerebellar lesions, and there have been reports of transient mutism and apathy occurring as part of a posterior fossa syndrome in children after resection of PFT. Possibly explaining this association, functional pathways have been described linking cerebellum to prefrontal regions associated with cognitive processes related to apathy.

It is among the youngest children that tumor management is particularly challenging and that the greatest long-term neurocognitive morbidity is observed. The current study focused on survivors who were <5 years of age at tumor diagnosis, rather than on older children. The aims of the study included determination of the extent to which clinically significant apathy was present in adulthood in the study population, investigation of the relationship between the presence of apathy and a possible diagnosis of depression, and an examination of possible treatment and cognitive factors associated with a risk of apathy in these adult survivors of a PFT diagnosed in early childhood/infancy.

Methods

Study Design

With use of established instruments in face-to-face interviews, this study assessed current apathy, IQ, and psychiatric diagnoses in as complete a sample of individuals meeting the study entry criteria as the authors could recruit across England. Similar assessments were undertaken in a comparison group comprising siblings of participating survivors. Adults aged at least 18 years at follow-up (2008–2010) who had received a diagnosis of a PFT before the age of 5 years during 1940–1991 were identified from the UK National Registry of Childhood Tumors and recruited through their general practitioners. A sibling comparison group was recruited through the index participants, with no more than one sibling recruited from each index participant (when >1 sibling was available, the one closest in age to the index participant was recruited when possible). Group comparisons adjusting for age and sex were performed using logistic regressions (to assess differences between higher and lower apathy groups) and multiple regression (to assess differences in group mean IQs).

Sample Size

The study aimed to recruit 120 survivors and a similarly sized sibling group. For a 2-tailed test with Type I error of 5%, this would provide 80% power to detect a difference in prevalence of a psychiatric diagnosis between survivor and sibling groups of 10%.

Approvals

The procedures followed in undertaking the study were in accordance with the ethical standards of the Helsinki Declaration (1964, amended 2008) of the World Medical Association. The study was approved by the Cambridgeshire 2 Research Ethics Committee, the National Information Governance Board (formerly the Patient Information Advisory Group, UK), and Primary Care Trust Research and Development committees covering those Trusts from which survivors were recruited. Those participants able to provide written informed consent did so. In addition, to minimize bias toward those survivors with better outcomes, participants lacking the capacity to consent to research were included when appropriate approvals were gained from family or care providers, in line with ss. 30–34 of the Mental Capacity Act (England & Wales) 2005.

Assessments

Apathy was assessed using the Marin Apathy Evaluation Scale (AES). This scale has 18 items, each rated from 1 to 4. It generates emotional, cognitive, and behavioral apathy subscale scores together with a full-scale score of 18–72, with higher scores reflecting increasing severity of apathy. It can be self-rated or scored through an informant. In this study, full-scale apathy scores will be presented. The AES has been widely validated with good reliability and validity in several clinical populations. However, no full-scale AES criterion score indicating clinically significant apathy has been reported for brain tumor survivors. Before the start of data collection, we therefore selected, for this purpose, a full-scale score of 34, considered by several authors as a criterion for a diagnosis of apathy, after a range of acquired brain insults in both male and female patients.

Participants also undertook standardized assessment measures comprising the Wechsler Abbreviated Scale of Intelligence to measure IQ and the Composite International Diagnostic Interview (CIDI) to assess current and lifetime psychiatric diagnoses. In this study, CIDI findings related to the possible presence of a current diagnosis of depression were considered. To achieve this, the following International Classification of Diseases, 10th Revision (ICD-10), depression diagnoses were included to determine whether ICD diagnostic criteria had been met for the presence of depression over the 30 days preceding assessment: severe depressive episode, moderate depressive episode, minor depressive episode. If participants were unable
to complete the CIDI because of cognitive limitations, a modified version of the Psychiatric Assessment Schedule for Adults with Developmental Disabilities (PAS-ADD)\(^\text{23}\) was used. Other data from the CIDI and PAS-ADD assessments will be reported elsewhere.

### Results

#### Recruitment

A total of 396 potential participants were identified from the UK National Registry of Childhood Tumors. The process of recruiting these, with numbers lost from recruitment, is shown in Fig. 1. Of 213 persons contacted via their GP, 118 took part, representing a 55% response rate, and of these, 117 completed the apathy assessment that is the focus of this paper. A comparison group comprising a sibling from 62 of these index participants was recruited, and 60 of these completed the apathy assessment.

#### Demographic and Clinical Characteristics

Mean age (± SD) of the 118 survivors at assessment was 35.4 ± 10.3 years and of the 62 siblings was 35 ± 10.8 years. There was no statistically significant difference between the mean ages of these groups (\(t = 0.213, df = 178, P = .832\)). Sex proportions were significantly different between the groups, with 42% of survivors being female, compared with 58% of siblings (\(\chi^2 = 4.461, df = 1, P = .041\)). Siblings had more years in education (\(t = -4.26, df = 156, P < .001\)), although this difference was small; siblings had a mean of 14.32 years in education, compared with 12.72 years for survivors.

In the survivor group, the mean age at tumor diagnosis was 39.0 ± 13.7 months. Tumor location was specified as cerebellum in 113 individuals, as cerebral ventricle in 2, and was unspecified (posterior fossa) in 3. Surgery was recorded for 104 of the survivors. In 45 individuals, this was described as total tumor removal and, in 36, as partial removal. Three individuals were recorded as having undergone palliative surgery and 2 as...
having only undergone a biopsy; in 18 cases, although surgery was received, its nature was unspecified. Radiotherapy was received by 74 individuals, 15 of whom also underwent chemotherapy. In the Registry database, treatment records were incomplete for 11 participants. Details of treatment received by those participants with the 2 most commonly recorded tumor types (medulloblastoma and astrocytoma) are outlined in Table 1.

AES Results

AES scores were obtained for 117 survivors and 60 of the siblings. Overall, survivors as a group obtained significantly higher full scale apathy scores than did the sibling comparison group (survivors: 32.2 ± 8.3; control group: 27.9 ± 6.0; t = 3.97, df = 175, P < 0.001). With respect to the prevalence of clinically significant apathy, full-scale apathy scores were ≥34, the predetermined criterion score for a diagnosis of apathy, in 35% of survivors, compared with 18% of the comparison group. These rates were significantly different even after group differences in age and sex were taken into account (odds ratio = 2.41; 95% confidence interval [CI] = 1.12–5.17; χ² = 5.49, df = 1, P = .02).

Relationship Between Apathy and Employment Status

There was a statistically significant relationship between apathy and employment overall, with those whose apathy scores reached criterion less likely to be employed (odds ratio = 2.49, 95% CI = 1.20–5.21; χ² = 5.91, df = 1, P = .015) after differences in age, sex, and study group were taken into account. Siblings were more likely to be employed (odds ratio = 2.41, 95% CI = 1.09–5.35; χ² = 5.01, df = 1, P = .025) even after differences in age, sex, and apathy were taken into account. No 2-way interactions were found between age, sex, apathy, and study groups and employment status.

Table 1. Treatments received by survivors for the 2 most common histological classes of tumors

<table>
<thead>
<tr>
<th>Tumor Typea</th>
<th>Medulloblastoma (n = 33)</th>
<th>Astrocytoma (n = 75)</th>
<th>P (Fisher’s exact unless specified)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiotherapy</td>
<td>28/33 had radiotherapy (85%)</td>
<td>40/75 had radiotherapy (53%). In 7 cases there was no record of whether radiotherapy was administered or not</td>
<td>0.03</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>10/33 had chemotherapy (no record for 5) (30%)</td>
<td>4/75 had chemotherapy (no record for 23) (5%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Partial or total resection</td>
<td>Of 23 people with extent of surgery specified, 12 had partial (52%) and 11 (48%) had total resection</td>
<td>Of 56 people with extent of surgery specified, 22 (39%) had partial resection and 34 (61%) had total resection</td>
<td>0.33</td>
</tr>
<tr>
<td>Gender</td>
<td>19 = male (58%)</td>
<td>45 = male (60%)</td>
<td>0.83</td>
</tr>
<tr>
<td>Age now</td>
<td>40.2 years (SD = 8.4)</td>
<td>32.6 (SD = 10.2)</td>
<td>P &lt; .001 (independent t-test)</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>41.8 months (SD = 10.38)</td>
<td>36.9 months (SD = 15.2)</td>
<td>P = .052 (independent t-test)</td>
</tr>
</tbody>
</table>

*Of the 9 remaining participants who completed the Apathy Evaluation Scale, 6 had a tumor described as an ependymoma, 2 had a subependymoma, and 1 had a spongioblastoma.

Mean IQ scores were significantly lower in the survivor group than in the comparison group (Table 2). However, no 2-way interactions were found between age, sex, apathy, and study group and IQ indices. Therefore, there was no difference between the survivor and the sibling groups with respect to the relationship between presence of apathy and IQ indices. In Table 3, the relationship between apathy state and IQ indices is described for the survivor group. Mean full-scale and verbal IQ, but not performance IQ, were significantly lower in apathy scorers reaching at least 34, compared with those who did not (Table 3).

Relationship Between Apathy and Sex

Using logistic regression, we found a greater likelihood for women to reach the apathy criterion relative to men if they were survivors (χ² = 17.85, df = 1, P < .001). Looking at male and female participants separately revealed that 36% of male siblings, compared with 28% of male survivors, reached the criterion score for apathy (χ² = 0.54, df = 1, P = .46), whereas 6% of female siblings, compared with 45% of female survivors, reached the criterion score for apathy (χ² = 17.85, df = 1, P < .001). Thus, among women, but not men, there was an excess of survivors reaching the apathy criterion. This difference between the groups in the relationship between sex and apathy was not related to IQ; the mean difference in full-scale IQ between males and females was not significantly different between survivors and siblings (F[1,170] = 2.71, P = .10), and there was no difference in the interaction of sex and full-scale IQ in predicting apathy in survivors,
Table 2. IQ differences between survivors and siblings

<table>
<thead>
<tr>
<th>IQ measure</th>
<th>Survivors Mean (SD)</th>
<th>Siblings Mean (SD)</th>
<th>Difference in group means adjusted for age and gender (Sibling – survivor)</th>
<th>Significance of group difference adjusted for age and gender (Multiple regression)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIQ</td>
<td>88.8 (18.2) (n = 111)</td>
<td>107.6 (11.8) (n = 60)</td>
<td>19.83, 95%CI = (14.81, 24.85)</td>
<td>t = 7.90, df = 1,170, P &lt; .001</td>
</tr>
<tr>
<td>VIQ</td>
<td>88.5 (16.6) (n = 112)</td>
<td>103.7 (12) (n = 60)</td>
<td>15.90, 95%CI = (11.17, 20.62)</td>
<td>t = 6.60, df = 1,171, P &lt; .001</td>
</tr>
<tr>
<td>PIQ</td>
<td>91.1 (18.2) (n = 110)</td>
<td>110 (12.3) (n = 60)</td>
<td>20.19, 95%CI = (15.15, 25.23)</td>
<td>t = 7.85, df = 1,169, P &lt; .001</td>
</tr>
</tbody>
</table>

FiQ, full-scale IQ; VIQ, verbal IQ; PIQ, performance IQ.

Table 3. IQ differences in the survivor group between those with full-scale AES score below and at or above criterion

<table>
<thead>
<tr>
<th>IQ measure</th>
<th>AES score &lt;34</th>
<th>AES score ≥34</th>
<th>Difference in group means adjusted for age and gender (non-apathetic – apathetic)</th>
<th>Significance of group difference adjusted for age and gender (Multiple regression)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIQ</td>
<td>92.0 (17.8) (n = 74)</td>
<td>81.9 (15.1) (n = 37)</td>
<td>9.40, 95%CI = (2.52, 11.92)</td>
<td>t = 2.73, df = 1,107, P = .007</td>
</tr>
<tr>
<td>VIQ</td>
<td>92.1 (16.7) (n = 74)</td>
<td>81.1 (13.8) (n = 38)</td>
<td>10.71, 95%CI = (4.45, 16.96)</td>
<td>t = 3.36, df = 1,108, P = .001</td>
</tr>
<tr>
<td>PIQ</td>
<td>93.4 (18.5) (n = 73)</td>
<td>86.3 (16.8) (n = 37)</td>
<td>5.70, 95%CI = (−1.49, 12.90)</td>
<td>t = 1.59, df = 1,106, P = .12</td>
</tr>
</tbody>
</table>

AES, Apathy evaluation scale; FIQ, full-scale IQ; PIQ, performance IQ; VIQ, verbal IQ.

compared with siblings ($\chi^2 [1] = 0.18, P = .67$). There were no other 2-way interactions found involving age, study group, and sex with apathy.

Relationship Between Apathy and Mood

Of the 101 survivors completing the AES and the CIDI, 7 met diagnostic criteria for an ICD depressive episode within the preceding 30 days, and 4 of these had a full-scale AES score reaching criterion, 2 of whom were female and 2 of whom were male. Of the 60 siblings interviewed using the CIDI, just one had a current depressive episode, and she also reached the AES criterion score. Of the 16 survivors interviewed using the PAS-ADD, 6 had current symptoms of depression compatible with an ICD diagnosis of depression, 3 of whom reached the AES criterion score.

Relationships Between Presence of Apathy and Brain Tumor–Related Variables in the Survivor Group

In the survivor group, exploratory $\chi^2$ analyses revealed that apathy reaching or exceeding the criterion score was not associated with tumor type (Fisher’s exact test, $P = .99$). In neither female nor male survivors was a history of having received radiotherapy associated with increased likelihood of having apathy meeting criterion (female survivors: $\chi^2 [1] = 0.246, P = .692$; male survivors: $\chi^2 [1] = 0.288, P = .592$). Among survivors for whom there were available data, 68% of men, compared with 67% of women, had previously received radiotherapy as part of their treatment. Although not associated with the presence of clinically significant apathy, in the survivor group, compared with those who had not received any radiotherapy, a history of radiotherapy was associated with significantly lower IQ scores (by ~10 points) (Table 4).

Neither age at tumor diagnosis ($t = 1.553; df = 115; P = .123$) nor time since diagnosis ($t = 1.159; df = 115; P = .249$) differed between those with and without apathy reaching criterion score. However, exploratory analysis found that 51% of those receiving partial tumor removal, compared with 24% of those who underwent total tumor removal, reached the apathy criterion score (Fisher’s exact test, $P = .019$). There was, however, no statistically significant difference in full-scale IQ between survivors who had partial (IQ = 89.6) and those who had total (IQ = 90.8) resections ($t = −0.303; df = 72; P = .763$).

To further investigate possible relationships between variables reflecting disease severity and treatment and outcomes in terms of prevalence and sex distribution of apathy in survivors, we undertook additional analyses after dividing the survivor cohort into 3 groups: (1) those with medulloblastoma ($n = 32$), (2) those with any astrocytoma and partial tumor removal who also received radiotherapy ($n = 15$), and (3) those with pilocytic astrocytoma who underwent total tumor removal and did not receive radiotherapy ($n = 15$). Although these additional comparisons only use small subsets of the study population, they provide a more detailed indication of the extent to which tumor type and treatment may be related to the development of subsequent apathy. As expected, radiotherapy was received more frequently by those with a medulloblastoma (and would most likely have been whole brain) and those with an astrocytoma only partially removed (most likely, focal cerebellar radiotherapy only) than by those with a completely removed astrocytoma ($\chi^2 [2] = 43.421, P < .001$). However, apathy was not observed less frequently in those with a completely removed astrocytoma than in the other 2 irradiated groups. Despite their higher IQ; in group 1 (as defined above), apathy was present in 31% of survivors, in group 2, it was present in 53%,
and in group 3, apathy was present in 40% ($\chi^2 [2] = 2.113, P = .348$). This analysis suggests that the presence of apathy reaching the threshold score of 34 is not associated with disease or treatment severity, as reflected by this categorization of brain tumor survivors. In addition, women were not over-represented among survivors with medulloblastoma, compared with those with astrocytoma, or among those with astrocytoma having partial as opposed to total tumor removal.

Comparison of Findings from Survivors with and without Sibling Controls

In the above analyses, to maximize power and use findings from all the survivors providing data for the study, we combined data from the 62 survivors who provided a sibling control and the remaining 56 survivors who did not. To check for possible bias in including these additional survivors, $t$ tests and $\chi^2$ tests were performed on various outcome measures used in this article. No differences were found between the 56 unpaired survivors and the 62 survivors with siblings in mean full-scale, verbal, or performance IQ; mean age; sex proportions; proportions with apathy scores $\geq 34$; or proportions receiving radiation treatment.

Nonresponder Analysis

A non-responder analysis was conducted to examine the representativeness of the participants in the current study with respect to the wider population of survivors of an early childhood cerebellar tumor. This analysis used data sets extracted anonymously from the National Registry of Childhood Tumors to compare sex, age at diagnosis and at time of study, tumor type, and treatments received among 100 survivors who participated in the study and 249 individuals who would have met the study entry criteria but did not participate. These characteristics were similar across those who did and those who did not take part in the study (Supplementary data table – on-line only file).

Discussion

In this study, the presence of apathy in a group of survivors of an early childhood PFT was investigated. Participants received a diagnosis before the age of 5 years and had survived until the age of $\geq 18$ years. Although several reports have noted the transient appearance of apathy, as part of a posterior fossa syndrome, soon after cerebellar surgery in children.\textsuperscript{13–15} The authors are unaware of any previous study that has investigated apathy in adult survivors of such early childhood PFTs. We have shown that a history of PFT diagnosed before the age of 5 years was associated with an increased risk of having clinically significant apathy when assessed at least 13 years later, compared with a sibling comparison group. The importance of identifying the presence of such apathy (defined as a full-scale AES score reaching the criterion of 34) is highlighted by the relatively high rate of 35%, of this condition in the survivors, and our observation that apathy was associated with being less likely to be in employment or education.

We also investigated possible associations of apathy in the survivor and sibling groups. Significant intellectual impairments have previously been reported within 5–10 years of treatment in up to 90% of survivors of brain tumors.\textsuperscript{24,25} Identified risk factors associated with poor long-term intellectual outcome include radiotherapy (site, dose, and fractionation schedule) as the most potent single cause\textsuperscript{26,27} and younger age at treatment, female sex,\textsuperscript{28} time since treatment, extent of cranial surgery,\textsuperscript{29} and chemotherapy.\textsuperscript{30} An examination in the current study of whether there was an association between apathy and IQ demonstrated that, although survivors with significant apathy had lower full-scale and verbal IQ scores than did those with apathy scores below the criterion, a similar pattern was observed in the sibling group, suggesting that lower IQ alone does not explain the greater apathy rates in brain tumor survivors.

Also differing between survivor and sibling groups was the relationship between sex and the presence of apathy. In studies of healthy older persons,\textsuperscript{31} apathy has been reported more often in men than in women. In the current study, however, being a survivor increased the risk of apathy in women but not in men. These results extend previous findings indicating worse intellectual and neuroendocrine outcomes after childhood cancer in females, suggesting that female sex may be a risk factor for a range of poor neuropsychiatric outcomes after childhood brain tumors and their treatment. However, unlike previous findings among central nervous system cancer survivors, in the current study,

### Table 4. Tested IQ scores in survivors with and without a history of having received radiotherapy

<table>
<thead>
<tr>
<th>IQ measure</th>
<th>Treatment group</th>
<th>n</th>
<th>Mean (SD)</th>
<th>Difference in group means adjusted for age, gender and apathy (no radiotherapy – radiotherapy)</th>
<th>Significance of group difference adjusted for age, gender and apathy (Multiple Regression)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full scale IQ</td>
<td>No radiotherapy</td>
<td>32</td>
<td>96.6 (14.7)</td>
<td>14.69, 95% CI = (8.09, 21.29)</td>
<td>$t = 4.45, df = 98, P &lt; .001$</td>
</tr>
<tr>
<td></td>
<td>Radiotherapy</td>
<td>72</td>
<td>84.5 (17.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>No radiotherapy</td>
<td>33</td>
<td>93.4 (14.5)</td>
<td>10.00, 95% CI = (6.92, 13.08)</td>
<td>$t = 3.25, df = 99, P = .002$</td>
</tr>
<tr>
<td></td>
<td>Radiotherapy</td>
<td>72</td>
<td>85.6 (16.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Performance IQ</td>
<td>No radiotherapy</td>
<td>32</td>
<td>99.2 (15.8)</td>
<td>14.22, 95% CI = (7.24, 21.20)</td>
<td>$t = 3.99, df = 97, P &lt; .001$</td>
</tr>
<tr>
<td></td>
<td>Radiotherapy</td>
<td>71</td>
<td>86.8 (18.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
there was no evidence that worse outcome in female survivors, in terms of risk of apathy, was explained by a history of radiotherapy. The basis of female predisposition to early physiological insult remains unknown. Armstrong and colleagues have suggested that sex-based differences in DNA repair enzymes would provide a model for a female predominance of inferior long-term outcomes but could identify no evidence to support this hypothesis.

Individual symptoms in syndromes of apathy and depression may overlap, and the validity of distinguishing apathy from depression has been questioned. We therefore investigated whether apathy as observed in the current study was associated with comorbid depressive illness. However, only small numbers of participants were found to have a concurrent diagnosis of depression, with no evidence that group and sex differences in apathy rates could be explained by distribution of depression diagnoses.

Associations between the presence of significant apathy and tumor type or treatment were also investigated. Apathy was present in similar proportions in survivors of the 2 most common classes of tumors: medulloblastomas and astrocytomas. Despite the expected observation in the survivor group that those who received radiotherapy had ~10 point lower IQ scores than did those who had not and the observation that patients with apathy reaching criterion had ~10 point lower IQ than did those without apathy, radiotherapy was not independently associated with subsequent apathy in adulthood. The observation that apathy was associated with having undergone partial rather than total tumor resection was not unexpected, and we can offer no explanation from our limited treatment data. Future research should seek to validate this observation with a more detailed analysis of extent of cerebellar surgery, operability, malignancy/histology of tumor, and postoperative complications, especially the presence and severity of any posterior fossa syndrome or mutism.

Increased risk of apathy among adult survivors of a childhood PFT is compatible with current knowledge regarding the cerebellum and its functions. It has been increasingly recognized as playing a role in cognitive and affective processes and neuropsychiatric symptoms, including depression, anxiety, and irritability. Language, visual-spatial, memory, and attentional deficits, together with irritability and emotional lability, have been reported in children undergoing cerebellar resections, with posterior fossa syndrome particularly associated with more extensive damage to the cerebellar vermis. Unfortunately, in the current study, we do not have details of precise tumor location in the cerebellum or data on whether participants of the current study had experienced a posterior fossa syndrome after their childhood surgery; therefore, we cannot determine whether the apathy that we have observed in subsequent adult life is related to having experienced transient apathy with mutism in childhood. However, in the series reported by Catsman-Berrevoets and Aarsen (2010), posterior fossa syndrome was observed in 28% of their patients, and in the current study, apathy reached criterion score in 35% of survivors. The approximate similarity of these 2 proportions suggests that the possible long-term sequelae of the posterior fossa syndrome should be urgently examined.

Several cautions apply to this study. Choice of an appropriate comparison group for studies of long-term outcomes of childhood experiences is difficult. A sibling comparison group, as also used by the North American Childhood Cancer survivor study, helps control for shared genetic and sociodemographic risk factors for development of psychopathology. However, siblings of survivors of a childhood cancer may have relatively high rates of psychopathology, including anxiety and excessive alcohol consumption in adulthood. The surprisingly high apathy rate noted in male siblings in the current study could be related to such effects but also to the apathy criterion score selected. Other studies have used different cutoff scores, and there is no gold standard. For instance, Brodaty et al. used a higher AES criterion score, derived from healthy controls, of 37. Use of that criterion in the current study would have given a male sibling apathy rate of 12% (and 8% across all siblings, with an apathy rate among survivors of 28%). The final response rate of 55% was relatively low. We nevertheless obtained apathy measures from 117 survivors of a childhood brain tumor, finding more apathy than in a sibling comparison group, and we think that it is unlikely that our sample overestimated prevalence of apathy. In addition, the nonresponder analysis revealed that participants of the current study resembled the wider population of survivors of an early childhood cerebellar tumor in terms of sex, age at diagnosis and at time of study, tumor type, and treatment. Although there are various apathy rating instruments, of the 15 examined by Clarke et al. (2011), the most psychometrically robust was the AES, as used in this study, and the apathy subscale of the Neuropsychiatric Inventory. However, the AES only elicits scores for the previous month. We cannot therefore make any comments regarding the duration of the apathy symptoms noted.

We consider that the results of this study are important, because apathy is often an insidious process that may be difficult to diagnose. Lack of clarity over the definition of apathy may also have the consequence of making it easier for clinicians and researchers to disregard. However, apathy syndromes may be potentially treatable, and our finding of apathy in 35% of a group of adult survivors of an early childhood PFT, with a particularly high rate among female survivors, should alert clinicians to keep this syndrome in mind when considering impaired functional outcomes in this clinical group.

Supplementary Material

Supplementary material is available online at Neuro-Oncology (http://neuro-oncology.oxfordjournals.org/).
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