AN EXAMINATION OF OBESITY IN PEDIATRIC BRAIN TUMOR SURVIVORS: FOOD FOR THOUGHT

A Thesis submitted to the University of Arizona College of Medicine -- Phoenix
in partial fulfillment of the requirements for the Degree of Doctor of Medicine

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Class of 2015

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Abstract

Background: Great strides have been made in childhood cancer treatment efficacy over the past two decades leading to improved survival rates, and now attention is being directed toward identifying and understanding complications that affect many of these patients as they reach adulthood. Obesity is a well-recognized late effect that has many potential long-term consequences some of which include cardiovascular disease, type II diabetes mellitus, dyslipidemia and even death. **Materials/Methods:** We conducted a retrospective chart review to determine the prevalence of obesity among survivors of pediatric brain tumors 5 years after the completion of therapy and compare this to the general pediatric population of the same age. We also sought to identify potential risk factors for the development of obesity among survivors of childhood brain tumors. Obesity was defined as a body mass index (BMI) greater than the 95th percentile for age and gender as defined by the most recent Center for Disease Control growth curves. **Results:** We identified 96 patients who met our inclusion criteria, however only 43 had follow-up data at 5 years after the completion of therapy to be included in final analysis. Of 43 patients, 5 (11.63%) were obese 5 years after completion of therapy. The CDC sites general population obesity rates in three age groups: 2-5 years (8.4% obesity rate), 6-11 years (18% obesity rate), 12-19 years (21% obesity rate). Using CDC guidelines, we found no significant difference between the obesity rate among the brain tumor survivor population for each age group and the general population, p-values of 0.865, 0.865, and 0.249 respectively. **Conclusion:** Our small sample size was likely not adequate to find a significant difference between the two groups or identify risk factors associated with the development of obesity. Larger studies are needed to further examine the risk of obesity among pediatric brain tumor survivors and to identify risk factors associated with this late effect.

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Introduction/Significance

Brain tumors are the most common solid neoplasm among the pediatric population affecting more than 4,000 children in the US each year.[1] Over the past 20, years advancements in therapies have led to improved overall survival for these patients.[2] It is now estimated that 1 in 1,000 adults between the ages of 20 and 30 years are survivors of childhood cancer.[3] With this improvement in survivorship comes an increased morbidity as the late effects of cancer therapy are becoming better understood. It has been well established that chemotherapy and radiation have profound effects on a child's neuroendocrine systems, growth, and neurocognitive development.[4]

Childhood obesity has more than doubled in children and quadrupled in adolescents in the past 30 years.[5,6] For children 2 to 20 years old obesity is defined as having a body mass index (BMI) at or above the 95th percentile for children of the same age and sex.[7] Childhood obesity presents immediate health risks for children including high blood pressure and high cholesterol, breathing problems such as sleep apnea and asthma, joint problems, gastro-esophageal reflux (heartburn), as well as potential social and psychological problems including discrimination and low self-esteem.[7] Obese children are also at a much greater risk for being obese in adulthood which is associated with several adverse health effects such as metabolic syndrome, cardiovascular disease, type 2 diabetes, certain cancers, and sleep apnea among others.[8]

Children diagnosed with brain tumors typically undergo a variety of aggressive cancer therapies that can produce late effects including metabolic and endocrine disturbances.[9] Previous studies have indicated that childhood brain tumor survivors have an increased risk of obesity and metabolic syndrome.[10] Metabolic syndrome is a constellation of findings that include: central or abdominal obesity, elevated triglycerides, low HDL cholesterol, high blood pressure, and elevated fasting glucose.[11] An adult with three or more of these risk factors could be diagnosed with metabolic syndrome however the definition for children and adolescents is not as well defined.[10] It is becoming more apparent the endocrine system is very sensitive to cancer therapies, in particular chemotherapy and radiation.[3] Increasing survival for childhood cancer patients is associated with both short and long-term morbidity including obesity,

disorders of lipid metabolism and numerous other disorders related to neuroendocrine dysfunction.[3]

With the known health risks of obesity as well as the potential for cardiotoxicity with some chemotherapeutic agents, childhood brain tumor survivors are likely at an increased risk for cardiovascular disease, as well as other serious health conditions associated with obesity.[12] The mechanism of altered metabolism and the development of obesity in these patients is not well understood and is likely multifactorial involving disease-related, treatment-related, genetic, as well as lifestyle factors.[9] Increased knowledge about risk factors for obesity in brain tumor survivors may lead to a better understanding of its development, and therefore could lead to its prevention.

Research Materials and Methods

We sought to determine the prevalence of obesity 5 years after the cessation of cancer therapy among a population of pediatric brain tumor survivors and compare it to the general pediatric population as defined by the CDC. We also sought to identify potential risk factors for the development of obesity among survivors of childhood brain tumors. The risk factors examined include age at diagnosis, gender, tumor histology, tumor location, treatment (surgery, chemotherapy, radiation), and presence of an endocrinopathy after therapy.

We review the charts of patients diagnosed with brain tumors between the ages of 2 and 15 years at Phoenix Children's Hospital between the years of 1995-2006. Exclusion criteria included: patients with tumors located within the hypothalamic-pituitary axis (HPA) including, but not limited to, craniopharyngiomas and pituitary adenomas. These tumors were excluded because they are known to cause "hypothalamic" obesity due to their disruption of the satiety center in the ventromedial hypothalamus and the hormonal regulation of the hypothalamic-pituitary axis.[13] Patients with spinal tumors, including spinal metastasis were also excluded.

Patients were de-identified and any identifying information was kept in a separate, secure location made unavailable to anyone other than for the purpose of the study. The following data was sought to be collected from each chart: 1) Age at diagnosis 2) Height and weight at diagnosis 3) Patient gender (M/F) 4) Tumor location (posterior/cerebellar, other) 5) Histology of tumor 6) Surgical treatment (extent of surgery: biopsy, partial resection, total resection) 7) Chemotherapy (Y/N) 8) Radiation (None/Focal/Craniospinal) 9) Long term medications (e.g. steroids, hormones, etc.) 10) Date completed treatment 11) Height and weight annually for 5 years after completion of treatment. BMI was calculated by the standard formula: BMI = weight(kg)/(height[m])^2. The most recent BMI growth curves developed by the CDC were used to determine the BMI percentile for each patient based on their age and gender.[7]

There were originally 6 defined histological categories: Medulloblastoma, low grade glioma, high grade glioma, germ cell tumor, ependymoma, and other which incorporated all histological types included in the study that did not fall into the previously listed categories. However, due to the small number of patients within the 4 latter subtypes, they were

combined into one histological category of 'other' for the purpose of analysis. Presence of endocrinopathy was determined based on the need for hormone replacement therapy (with the exception of oral contraception) after completion of cancer therapy.

Statistical Analysis

The prevalence of obesity among brain tumor survivors in each age group was compared to the estimated rates for the general population of the corresponding age groups with proportion calculations. Categorical variables: age at diagnosis (three groups), gender, tumor location, tumor histology, extent of surgery, chemotherapy, radiation, and presence of endocrinopathy after therapy were analyzed using Fisher's exact test. A p-value <0.05 was considered significant and p-values reported are two-sided. All statistical analyses were performed using STATA for windows version 13.1.

Results

We reviewed the charts of 96 patients who met study criteria, 43 of whom had follow-up 5 years after the completion of therapy with height and weight recorded from which a BMI could be calculated. There were several patients for whom full data sets could not be gathered secondary to either poor documentation, lack of follow-up or transfer of care to other healthcare providers in different systems for which records could not be accessed. The prevalence of obesity based on BMI percentile for our cohort was compared to the prevalence of obesity among the general American pediatric population for similar age groups as cited by the CDC. The prevalence of obesity among the general pediatric population, as cited by the CDC, is estimated to be 8.4% in children 2-5 years old, 18% in children 6-11 years old and 21% in adolescents 12-19 years old.[5]

Among the population of brain tumor survivors with 5 year follow-up data, 13 were in the 2-5 year age group. One (7.14%) of the 13 was calculated to be obese 5 years after completion of therapy. When compared to the general population estimation of 8.4% for the same age group as cited by the CDC[5], we found no significant difference between the two groups (p-value 0.865). There were 24 individuals between the ages of 6 and 11 with 5 year follow-up data available. Of those 24, 4 (16.67%) were noted to be obese 5 years after completion of therapy. When compared to the general population estimation for the same age group of 18% as cited by the CDC [5], no significant difference was found between the two groups (p-value 0.865). In those aged 12-19 years, there were 5 individuals with 5 year follow-up data after completion of therapy. Of those 5 individuals, none (0.0%) were obese. When compared to the general adolescent population estimation of 21% as cited by the CDC[5], no significant difference was found between the two groups (p-value 0.249). These results are displayed in table 1.

Table 1. Prevalence of obesity among pediatric brain tumor survivors compared to that of the general pediatric population by age group

Age group (years)	Obesity rate, PBTS* (n)	Obesity rate, GP**	P-Value
2 to <6	7.14% (1/13)	8.4%	0.865
6 to <12	16.67% (4/24)	18%	0.865
12 to <20	0.0% (0/5)	21%	0.249

*PBTS: pediatric brain tumor survivors

**GP: general population

We also sought to determine if age at diagnosis, gender, tumor location, tumor histology, extent of surgery, chemotherapy, radiation, or presence of endocrinopathy after completion of therapy had an effect on the development of obesity among survivors of pediatric brain tumors. We found no significant association between any of these factors and the development of obesity (p-value <0.05), results are displayed in table 2.

Table 2. Patient characteristics by proportion of obese and non-obese 5 years after completion therapy

Variable	Obese (n)	Non-Obese (n)	P-Value
Age at Diagnosis (years)			0.809
2 to <6	1 (7.14 %)	13 (92.86 %)	
6 to <12	4 (16.67 %)	20 (83.33 %)	
12 to <20	0 (0.00 %)	5 (100.00 %)	
Total	5 (11.63 %)	38 (88.37 %)	
Gender			1.000
Male	3 (13.04 %)	20 (86.96 %)	
Female	2 (10.00 %)	18 (90.00 %)	
Total	5 (11.63 %)	38 (88.37 %)	
Tumor Location			0.575
Posterior/cerebellar	3 (9.09 %)	30 (90.91 %)	
All other	2 (20.00 %)	8 (80.00 %)	
Total	5 (11.63 %)	38 (88.37 %)	
Tumor Histology			0.400
Medulloblastoma	1 (5.56 %)	17 (94.44 %)	
Low grade glioma	4 (20.00 %)	16 (80.00 %)	
Other	0 (0.00%)	5 (100.00 %)	
Total	5 (11.63 %)	38 (88.37 %)	
Surgery			0.241
Biopsy	0 (0.00 %)	1 (100.00 %)	
Partial resection	2 (33.33 %)	4 (66.67 %)	
Gross total resection	3 (8.33 %)	33 (91.67 %)	
Total	5 (11.63 %)	38 (88.37 %)	
Chemotherapy			1.000
No	2 (10.00 %)	18 (90.00 %)	
Yes	3 (13.04 %)	20 (86.96 %)	
Total	5 (11.63 %)	38 (88.37 %)	
Radiation			0.570
None	3 (16.67 %)	15 (83.33 %)	
Focal	1 (14.29 %)	6 (85.71 %)	
Craniospinal	1 (5.56 %)	17 (94.44 %)	
Total	5 (11.63 %)	38 (88.37 %)	
Endocrinopathy			0.145
No	5 (17.86 %)	23 (82.14 %)	
Yes	0 (0.00%)	15 (100.00 %)	
Total	5 (11.63 %)	38 (88.37 %)	

Discussion

The prognosis for individuals diagnosed with childhood cancers has greatly improved over the past 20 years, however this increase in survival has not been without the recognition of serious late effects of cancer therapies.[14] Improvements in cancer treatment have been achieved at a cost with survivors facing significant long-term.[3,14] In this study we sought to determine the prevalence of obesity 5 years after the cessation of cancer therapy among a population of pediatric brain tumor survivors and compare it to that of the general pediatric population. We found that obesity rates among the brain tumor survivor population for each age group were not significantly different from that of the general population. Previous studies that have looked at obesity among survivors of childhood cancers have noted there to be an increased rate of obesity among survivors of childhood cancers, particularly survivors of acute lymphoblastic leukemia and brain tumors.[4,10] Though our results do not reproduce these findings, this could be explained by our small sample size and limited years of follow-up. We examined only a small number of survivors for a short period of time after cessation of therapy. With 43 brain tumor survivors having 5 year follow-up data, and 5 of those individuals being obese at 5 years after therapy, the sample size is not adequate to show a difference between the two populations if one exists. It has been demonstrated in previous studies that survivors of childhood malignancies are at greater risk for complications, including obesity and require long-term surveillance.[4,14] Although the timeframe during which the obesity risk increases and may become notable has not been well defined, the recommendation has been made by some that these patients be monitored long-term, as these late effects of treatment may not become apparent until adulthood.[3] It is likely that 5 years after the cessation of treatment is not long enough to identify those individuals at risk.

We also examined whether or not age at diagnosis (three groups), gender, tumor location, tumor histology, extent of surgery, chemotherapy, radiation, and presence of endocrinopathy after therapy had any effect on the development of obesity. None of these variables was found to be associated with an increased rate of obesity. Previous studies have found patients diagnosed at a younger age, and those who received chemotherapy or craniospinal radiation to be a greater risk of late effects, particularly endocrinopathies,

metabolic syndrome and obesity.[3,14,15] Though our population does not show similar risk, this could again be explained by our small sample size compared to other studies. With 5 of 43 brain tumor survivors being obese at 5 years after therapy, this was not a sufficient number to find significant associations between any variables as risk factors and an increased rate of obesity. Furthermore, it is unclear how long it takes for these late effects to appear and it may not be until adulthood.[3] Thus it is import to follow these patients long-term to survey for complications and to continue to assess and better understand the risk factors associated with these complications.

The variables we chose to examine were either variables that had been studied previously and shown to have association with the development of obesity or ones that logically related to weight gain. For example, it seems likely that disruption of the neuroendocrine system (endocrinopathy) could lead to the development of obesity, as it had been described that craniopharyngiomas and disruption of the hypothalamic-pituitary axis lead to the development of obesity.[16] However, again, our sample size was small and could be the reason why we were unable to demonstrate an association between endocrinopathy after treatment and obesity. Similarly, some studies had demonstrated association with craniospinal radiation and obesity.[3,13] However both radiation and chemotherapy have had mixed findings in the literature as to whether they contributes to the development of obesity. Some studies have demonstrated that higher doses of craniospinal radiation often disrupt growth and can have an effect on the development of obesity among pediatric brain tumor survivors.[14,15] Other studies have demonstrated that only when the hypothalamic-pituitary axis receives high doses of radiation that causes endocrine abnormalities after treatment did survivors develop obesity.[10] We were unable to find any effect on the development of obesity from radiation or chemotherapy treatments. Again, our sample size is small and this could explain our inability to find an association between these variables and the development of obesity.

We found no significant difference in the rate of obesity among survivors of pediatric brain tumors and the general pediatric population. We also found no variables that had an effect on the development of obesity among pediatric brain tumor survivors. A larger study is

likely needed to identify if there is an increased rate of obesity among survivors of pediatric brain tumors and to identify risk factors for the development of obesity in this population.

Future Directions

New, larger studies are needed to further evaluate late effects childhood brain tumor survivors face, the risk factors associated with them and the time frame during which these effects begin to become problematic. Understanding this could lead to the ability to intervene and improve quality of life, morbidity and mortality later in life for these survivors. It is clear after examining our cohort that future studies involving larger sample sizes, observed for a greater number of years after completion of treatment are necessary.

Conclusions

With an increased number of childhood brain tumor survivors reaching adulthood, an increased awareness and understanding of the late effects they face in as adults is essential. The complications of childhood cancer and cancer therapies may have an impact on quality of life, morbidity and mortality. Therefore it is crucial that these survivors have long-term and possibly lifelong follow-up. Though this study had an inadequate sample size to find a significant different between rates of obesity among pediatric brain tumor survivors and the general pediatric population or identify risk factors for obesity, previous studies have demonstrated this. It is important that future studies continue to examine the risk factors related to obesity among pediatric brain tumor survivors and that interventions to prevent complications for these survivors are explored.

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