

Pituitary Hormone Dysfunction after Proton Beam Radiation in Children with Brain Tumors

Running title: Endocrinopathies After Cranial Radiation

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Abstract:

Objective: To characterize endocrine dysfunction in pediatric brain tumor patients who received proton beam (PB) radiation, and to compare those treated with PB alone vs combined conventional and PB (Con/PB) radiation.

Methods: A retrospective chart review of patients ≤ 18 years of age who received PB radiation for a brain tumor from 2000-2008 was performed. Variables analyzed included patient demographics, tumor type, therapeutic modalities, radiation doses, and types and timing of endocrine dysfunction.

Results: Thirty eight patients were identified, of whom 31 aged 11.8 ± 3.3 years (19 girls) had undergone endocrine evaluation. Of these, 19 received PB and 12 received Con/PB radiation. Cranial surgery was performed in 28 subjects, and 25 received chemotherapy. Average length of follow-up since radiation was 1.8 ± 0.8 years. Nine (47%) patients in the PB and four (33%) in the Con/BP group developed endocrine dysfunction ($p=ns$) following cranial irradiation. Although total radiation doses between the groups did not differ, children with endocrine sequelae treated with PB received fewer cobalt grey equivalents (CGE) than those treated with Con/PB (5384 ± 268 vs 5775 ± 226), $p < 0.01$) and pituitary hormone deficiencies were detected later (1.17 ± 0.4 years vs. 0.33 ± 0.11 years, $p < 0.01$).

Conclusions: A high rate of endocrine sequelae was seen in our study. Children treated with Con/PB developed endocrine dysfunction faster and received more radiation than those in the PB group. Surgery and chemotherapy were additional risk factors. Large prospective studies are needed to further evaluate the incidence of endocrine sequelae following PB radiation in children.

Introduction:

Brain tumors comprise approximately 17% of all malignancies in patients younger than 20 years of age. The treatment of these tumors includes surgery, chemotherapy, and radiation, all of which are associated with a high risk of endocrine sequelae. Radiation specifically is associated with high rates of hypothalamic pituitary dysfunction (1). Up to 70% of children who receive radiation therapy develop anterior pituitary hormone dysfunction (2) and those who receive >4000 cGy are at risk for multiple pituitary hormone deficiencies (MPHD) (1,3-4). Historically, nearly 100% of children treated with conventional radiation over 3,000 cGy have developed growth hormone deficiency (5). Twenty to 50% of children end up with gonadotropin deficiency (1), and approximately 19% have hypothalamic-pituitary-adrenal axis abnormalities (6). Rates of central hypothyroidism following conventional radiation are reported to be anywhere between 6-36% depending upon the length of follow up (7). Overall 5 and 10 year survival rates for children with brain tumors have increased from approximately 60% to 75% over a 20 year period (8). As survival rates in children with brain tumors increase, the morbidity associated with treatment becomes more pronounced.

Proton beam (PB) radiation is a newer therapeutic modality that provides targeted delivery to the tumor site while reducing radiation exposure to normal tissues such as the hypothalamus and pituitary gland (9). This occurs because of a rapid fall in the radiation exit dose following maximal dose deposition at the target site (10). Theoretically, this type of radiation modality could prevent the development of neuroendocrine dysfunction. However, studies regarding endocrine deficits associated with this type of radiation, especially in children, are limited. At our institution, it has become standard practice to use proton beam radiation for all children who require radiation therapy. The use of conventional radiation is limited to those who are too

clinically unstable to travel to the proton beam radiation site. However, whether proton beam radiation truly reduces morbidity in childhood brain tumor patients is unknown.

In this study, our objective was to characterize the rate and type of pituitary hormone dysfunction in children with brain tumors who received PB. We then compared the rates and type of dysfunction in this population to children with brain tumors who received both conventional and proton beam radiation (Con/PB).

Materials and Methods:

Following institutional review board approval, we conducted a retrospective review of children ≤ 18 years old who underwent PB radiation between 1/1/2000-10/1/2008. Children were included if they had at least one subsequent follow up visit for cancer treatment at our institution, and had been evaluated for endocrine abnormalities. From the hematology/oncology and endocrinology medical records, we extracted the following variables: age, gender, race, tumor type, type of therapeutic modalities including surgery and chemotherapy, dose of PB, dose of Con radiation, and presence and time to development of pituitary hormone deficiency.

As some of the patients had received PB radiation alone, and some had received both Con and PB, they were separated into two groups based upon the type of radiation exposure. Cobalt gray equivalents (CGE) were based on the uniform relative biological equivalence of 1.1 for protons (11). In accordance with the radiation oncology literature, cGy and CGE doses were considered equivalent for the purposes of statistical analysis. The diagnosis of pituitary hormone dysfunction was based upon standard criteria. Specifically, children were diagnosed with growth

hormone deficiency if a peak stimulated growth hormone level was $< 10\text{ng/mL}$ (prior to 2005) or $<5\text{ng/mL}$ (after 2005) following the sequential administration of two secretagogues. Central hypothyroidism was diagnosed if the patient had a low free T4 level in the setting of a normal TSH. Central adrenal insufficiency was diagnosed if a patient had a peak stimulated cortisol level of $<18\text{ mcg/dL}$ following low dose (1 mcg) ACTH stimulation testing. Hypogonadotropic hypogonadism was diagnosed if patients had absent puberty by age 13 years in girls and 14 years in boys with low serum gonadotropin levels.

Statistical analysis:

Data are expressed as means \pm standard deviations. Independent-samples t tests (for continuous variables) and Fisher exact tests (for categorical variables) were used for comparisons between the two groups. P-values of <0.05 were considered significant.

Results:

Of the 38 patients who had received PB radiation, 31 (19 boys, 12 girls) had at least one formal endocrinology evaluation and were included in our analysis. Mean age of these patients at time of review was 11.9 ± 3.3 years. Mean length of follow up from PB radiation until the date of review was 1.8 ± 0.8 years. The most common brain tumor types were craniopharyngioma (n=7), medulloblastoma (n=6), and glioma (n=4). Twenty eight patients had surgery prior to radiation. Twenty two patients received chemotherapy prior to or with radiation therapy. The clinical characteristics of the patients are summarized in Table 1.

Of the 31 patients analyzed, 19 received only PB radiation and 12 received Con/PB radiation. Overall brain tumor locations did not differ among the two groups. Prior to radiation, eight patients in the PB group already had evidence of pituitary hormone deficiencies, two of whom

went on to develop additional endocrinopathies following radiation exposure. No pre-radiation endocrinopathies were noted in the Con/PB group. Of the remaining subjects, seven in the PB group and 4 in the Con/PB group developed pituitary dysfunction after radiation therapy (47% vs 33%, $p=ns$), four of whom had MPPHD. Of those who developed pituitary hormone dysfunction in the PB group, six had craniopharyngiomas, one child had a medulloblastoma, one had a glioma, and one had rhabdomyosarcoma. Specific abnormalities in the PB group consisted of GHD ($n=6$), TSH deficiency ($n=3$), ACTH deficiency ($n=3$), and hypogonadotropic hypogonadism ($n=3$). Of those with pituitary hormone deficiencies in the con/PB group, three children had medulloblastomas and one had a glioblastoma. Pituitary hormone abnormalities in this group consisted of ACTH deficiency ($n=3$), TSH deficiency ($n=1$), and hypogonadotropic hypogonadism ($n=1$). The distribution of these among the groups is illustrated in figure 1. Among those who developed pituitary hormone deficiencies these were detected sooner during follow up in the con/PB group than in the PB group (0.33 ± 0.11 years vs. 1.17 ± 0.4 years, $p<0.01$, figure 2A). The Con/PB group also received a higher dose of radiation than the PB group (5775 ± 226 CGE vs 5384 ± 268 CGE, $p<0.02$, figure 2B).

Discussion:

The goal of cranial radiation in pediatric brain tumor patients is to optimize treatment to the tumor site while sparing normal tissue. The advent of PB radiotherapy has been accompanied by significant optimism regarding its potential to favorably impact rates of endocrine late effects in childhood brain tumor survivors. Whether this promise will be realized is unknown. Thus far, minimal information regarding clinical outcomes in pediatric recipients of PB radiation is available. In one small study of children treated with PB radiation for germ cell tumors, 4/4 who did not have endocrine abnormalities at baseline developed them following radiotherapy (12). In

another group of 17 children with ependymomas, the use of PB radiation was associated with lower radiation doses and greater sparing of normal tissue than traditional radiation therapy. Although no late toxicity was reported, the specifics in terms of neuroendocrine evaluation in this group of patients was not provided (9). To our knowledge, ours is the first study to compare endocrine outcomes between a group of patients treated with PB radiation alone and a group receiving combined Con/PB radiation.

Several limitations to our study exist. In addition to radiation, the majority of our subjects underwent cranial surgery and received chemotherapy, both of which are notorious for increasing the risk of neuroendocrine problems (13-15). In addition, as evidenced by the presence of pre-treatment endocrinopathies in some of the subjects, brain tumors themselves can cause hypopituitarism (16). Thus, it is impossible to quantify the contribution of any one of these variables on the development of endocrine sequelae in these patients, and the risks attributed to PB radiation may be overestimated. Another limitation is that, due to its retrospective nature, the timing and type of endocrine evaluation in our cohort of children with brain tumors was not standardized. Not only could this lead to an underestimation of rates of neuroendocrine dysfunction, but the precise temporal relationship between a CNS insult such as cranial radiation and the development of an endocrinopathy in our subjects could not be determined. Lastly, our mean length of follow-up of approximately two years was short. Some pituitary hormone deficiencies associated with cranial irradiation, such as ACTH deficiency, can manifest up to 30 years after initial treatment (17). As a result, children who did not have pituitary hormone deficiencies at the time of our study may develop them in the future. Thus, our findings should be considered preliminary.

In 2009, there were five PB treatment centers in the United States that offered treatment for children with brain tumors. Four new centers were near completion in 2010 (18). The cost of these centers is 1.7 to 2.1 times greater than what would be seen with traditional radiation therapy (19), resulting in an increase in total health care costs for children with brain tumors. These health care costs could be reduced if there were further reductions in morbidity related outcomes or if the number of doses required to treat the primary tumor were lower (16). Further evaluation of treatment outcomes is needed evaluate the total cost/benefit ratio of PB radiation in childhood cancer patients.

In summary, we observed a high rate of presumed radiation induced pituitary hormone dysfunction in children receiving both PB alone and combined Con/PB radiation (47% and 33% respectively). These rates are similar to historical data of pituitary hormone deficiencies associated with conventional radiation at comparable doses (1,5,6,7). Interestingly, we detected endocrinopathies in children in the Con/PB group sooner than in the PB alone group. However, as these subjects also received more radiation than those in the PB alone group, it is difficult to attribute this difference to radiotherapy technique versus exposure. Regardless, our results suggest that children who undergo treatment with PB radiation for brain tumors represent a high risk population for developing pituitary hormone deficiencies. As PB radiation grows in popularity, larger prospective studies are needed to further evaluate its role in pediatric brain tumor therapy and exact relationship to the subsequent development of neuroendocrine dysfunction in these patients.

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Figure legends:

Figure 1A: Distribution of Pituitary Hormone Deficiencies in PB group (N=9)

Figure 1B: Distribution of Pituitary Hormone Deficiencies in Con/PB group (N=4)

Figure 2A: Time to Detection of Endocrinopathies in PB and Con/PB groups

Figure 2B: Radiation Doses Administered in PB and Con/PB groups

Abbreviations:

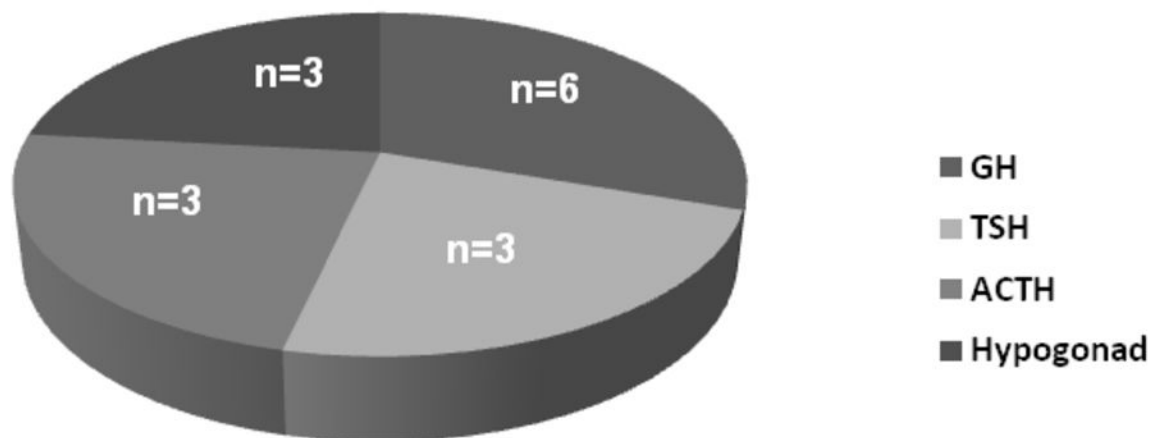
PB=proton beam radiation

Hypogonad=hypogonadotropic hypogonadism

MPHD=multiple pituitary hormone deficits

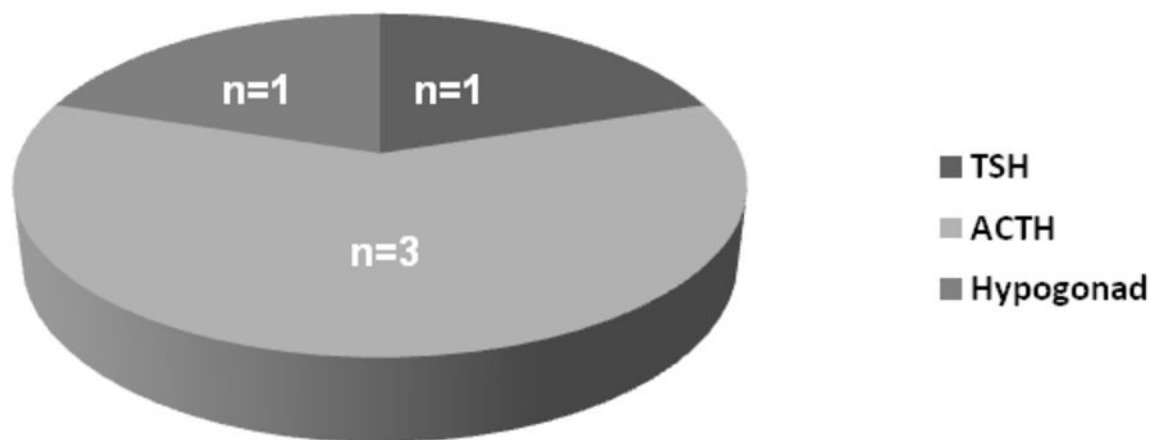
Con/PB=conventional and proton beam radiation

1A



3 with MPHD

1B



1 with MPHD

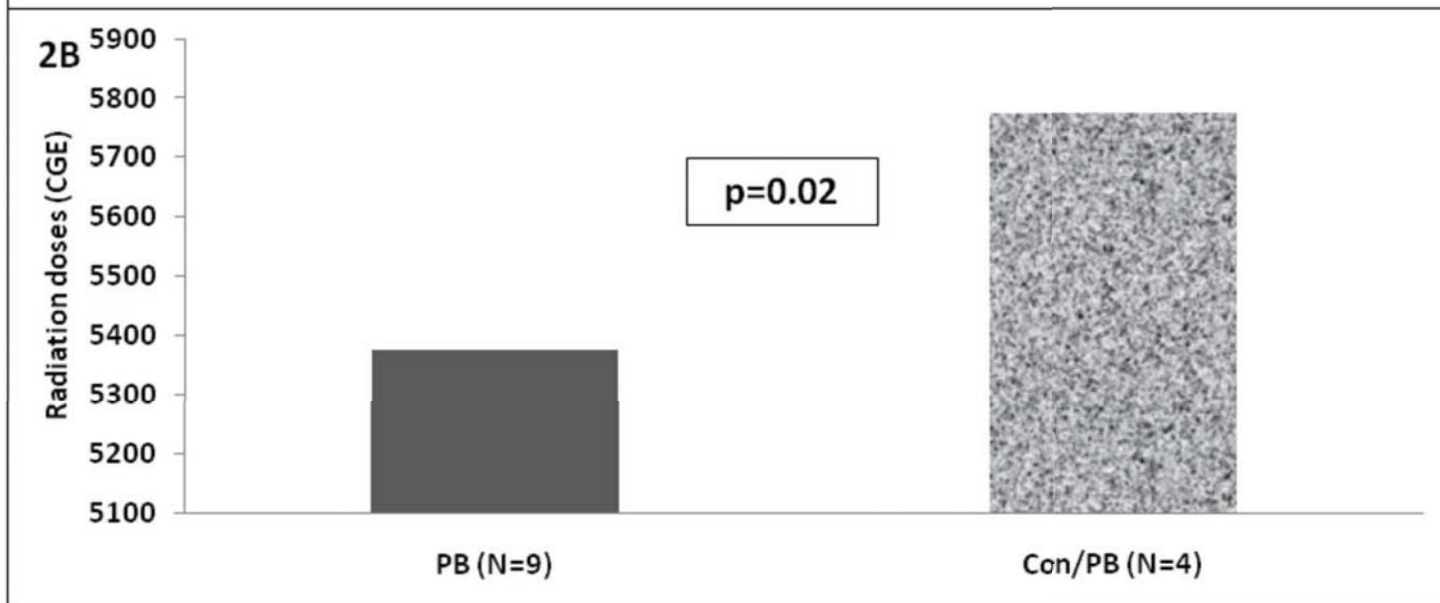
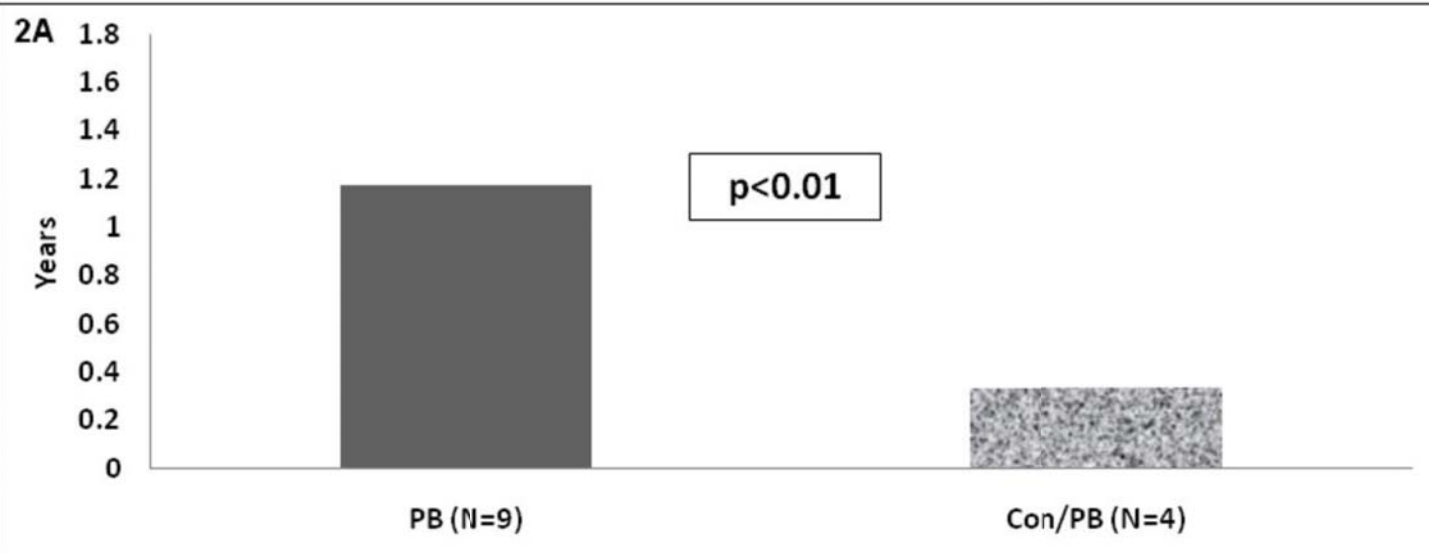


Table 1: Clinical characteristics of children who received proton beam radiation as part of brain tumor treatment

Characteristic		No. of cases
Sex	Boys	19
	Girls	
Age (years) and range		
10.1±1.5 (3.6-17.4)		19
14.8±3.9 (3.8-16)		12
Race		
White		29
Black		1
Hispanic		1
Tumor Type		
Craniopharyngioma		7
Medulloblastoma		6
Glioma		4
Rhabdomyosarcoma		3
Ependymoma		2
Astrocytoma		2
Primitive neuroectodermal tumor (PNET)		2
Retinoblastoma		2
Glioblastoma		1
Germinoma		1
Ewing sarcoma		1