

Osteopenia in Children Who Have Undergone Posterior Fossa or Craniospinal Irradiation for Brain Tumors

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Objectives: To determine lumbar spine and total body bone mineral density (BMD) in pediatric patients who have undergone cranial or craniospinal irradiation for posterior fossa tumors, specifically medulloblastoma and ependymoma and to analyze the association between degree of osteopenia and factors that may affect BMD.

Methods: Retrospective and prospective data collection included medical record review and examination, including pubertal, dietary, and activity assessment. Lumbar spine and total body BMD were measured by means of dual energy x-ray absorptiometry. Patients were routinely observed by the endocrinology department, and hormone deficiencies were corrected promptly. A subset of patients received calcium and vitamin D supplementation and underwent repeat BMD measurement 1 year later.

Results: Of 24 patients aged 4 to 20 years, 11 of whom were male, recruited from 1996 through 1999, 19 had medulloblastoma. All 19 underwent craniospinal radiotherapy plus a boost to the posterior fossa (mean \pm SD of 5410 ± 130 rad [54.1 ± 1.3 Gy] to the posterior fossa, mean \pm SD of 3470 ± 460 rad [34.7 ± 4.6 Gy] to the whole brain and spinal axis), and 8 of 19 underwent chemotherapy. The remaining 5 patients had ependymoma and underwent irradiation to the posterior fossa only (mean \pm SD of 5680 ± 720 rad [56.8 ± 7.2 Gy]). Therefore, there were 3 treatment groups: craniospinal irradiation and chemotherapy, only craniospinal irradiation, and only posterior fossa irradiation. Bone mineral studies were performed a mean \pm SD of 5.42 ± 3.23 years after therapy. Our patients had lower total body BMD (mean z score, -0.47 ; 95% con-

fidence interval, -0.85 to -0.09) and lumbar spine BMD (mean z score, -1.27 ; 95% confidence interval, -1.81 to -0.73) as compared with those of the general population. There was no significant difference in mean lumbar spine BMD between patients in the 3 groups. Our patients consumed a diet deficient in vitamin D and calcium (mean \pm SD $53.6\% \pm 24.1\%$ and $70.0\% \pm 37.4\%$ of the amount recommended, respectively). Of 7 patients who underwent measurements 1 year later, 5 had an increase in BMD that was parallel to normal curves, with no compensatory increase. Four patients were hypothyroid, 6 were growth hormone deficient, and 6 were both. All hormones were replaced, with the exception of growth hormone in 1 patient. By using regression analysis, the factors that affected lumbar spine BMD, protectively in both cases, were calcium intake ($\beta = 0.015$, 95% confidence interval, $0.001-0.029$) and female sex ($\beta = 1.422$, 95% confidence interval, $0.456-2.388$).

Conclusions: Children who have undergone irradiation for posterior fossa tumors have diminished total body and lumbar spine BMD, as compared with those of the general population. This reduction was similar within all 3 treatment groups, which suggests that chemotherapy did not play a major role and that localized irradiation may have systemic effects. This population often has balance and gait problems, so the risk of falling, coupled with osteopenia, may place them at considerably increased risk of fractures.

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CHILDHOOD IS AN IMPORTANT time for skeletal growth and bone mass deposition. Between the ages of 1 and 10 years, total bone density increases by 80%. An additional 50% increase occurs in adolescence, resulting in attainment of nearly maximal adult bone mineral density (BMD) by late adolescence.¹ Children with certain brain tumors undergo craniospinal irradiation to treat the tumor or to destroy presumed microscopic deposits,

which may potentially be a source of relapse. Craniospinal irradiation has been known for decades to cause slowed spinal growth, resulting in short stature.²

Results of a few studies suggest that radiotherapy to the brain may also cause decreased spinal bone mass, or osteopenia. Gilsanz et al³ described a significant decrease in lumbar trabecular BMD, measured by means of quantitative computed tomography, in children with acute lymphoblastic leukemia who had been treated with chemotherapy and radio-

therapy to the brain. The BMD in this group of patients was decreased relative to that in patients who underwent only chemotherapy. The fact that osteopenia was detected at a site distant from the site of irradiation suggests that radiotherapy, besides its local effects on bone growth, may also act systemically to reduce bone deposition or increase bone resorption. The authors speculated that reduced growth hormone production might have been responsible for BMD reduction.

In another study by Mithal et al,^{4,7} 7 adult survivors of childhood medulloblastoma had decreased BMD measured both in the lumbar spine and femoral neck by means of dual energy x-ray absorptiometry. These patients had undergone craniospinal irradiation a mean of 28 years before the study. Similar to the work of Gilsanz et al,³ results of this study demonstrated that radiotherapy may cause decreased BMD and that this decrease is not limited to the radiotherapy field.

The aim of our study was to determine lumbar spine and total body BMD in pediatric patients who had undergone posterior fossa or craniospinal therapy for posterior fossa brain tumors. If osteopenia was present, we also analyzed the association between the degree of osteopenia and other factors that may affect BMD, including age at the time of therapy, sex, calcium and vitamin D intake, activity level, and hormonal status. This population is of particular interest because many patients with posterior fossa tumors have gait disturbances, which, coupled with a risk of osteopenia, put them at higher risk of fractures. In addition, as noted, we assessed possible contributory factors such as hormonal and nutritional status that, if managed appropriately, might reduce the long-term morbidity of treatment.

METHODS

PATIENTS

Twenty-four patients who were treated in childhood with radiotherapy for posterior fossa brain tumors from 1987 through 1999 were recruited for our study from 1996 through 1999. Nineteen patients had medulloblastoma, and all underwent craniospinal radiotherapy consisting of a mean \pm SD of 5410 ± 130 rad [54.1 ± 1.3 Gy] to the posterior fossa and 3470 ± 460 rad [34.7 ± 4.6 Gy] to the whole brain and spinal axis. Eight of these 19 patients also underwent chemotherapy according to Pediatric Oncology Group Protocol, which included cisplatin, etoposide, vincristine sulfate, and cyclophosphamide. The remaining 5 patients had posterior fossa ependymoma and received a mean \pm SD of 5680 ± 720 rad [56.8 ± 7.2 Gy] radiation to the posterior fossa only and did not undergo chemotherapy.

In the interest of assessing the effect of different treatment modalities on bone density, our patients were placed into 1 of 3 groups: those who underwent limited volume posterior fossa irradiation that did not include the hypothalamic-pituitary axis (ependymoma), those who underwent only craniospinal irradiation (medulloblastoma), and those who underwent craniospinal irradiation and chemotherapy (medulloblastoma).

DATA COLLECTION

Retrospective and prospective methods of data collection were used. Medical records were reviewed in all patients. Each patient underwent physical examination including height, weight,

and pubertal status according to Tanner staging. The parents and/or patients were asked to complete a brief questionnaire about the patient's risk for osteoporosis, including information on diet, by using a 1-week food record, exercise, family history, medication use, and smoking. After initial investigations, all patients with diminished bone density received supplemental calcium and vitamin D, and a subset of patients agreed to undergo repeat bone densitometry 1 year later.

LABORATORY INVESTIGATIONS

Routine surveillance was performed in all children who had undergone cranial irradiation. Growth hormone levels were measured by using chemiluminescence (Nichols Institute Diagnostics, San Clemente, Calif). Growth hormone deficiency was defined on the basis of slow growth velocity (less than 2 SDs less than the mean for age and pubertal status) and results of 2 growth hormone stimulation tests with L-arginine hydrochloride or clonidine hydrochloride and a peak growth hormone value less than 8 ng/mL (352 pmol/L). As a basic screen for metabolic bone disease, we requested testing of serum calcium, magnesium, phosphorus, and alkaline phosphatase levels and a random check of urinary calcium and creatinine levels.

The patients' dietary calcium intake was expressed as a percentage of dietary reference intake (DRI).⁵ The patient's dietary vitamin D intake was expressed as a percentage of the recommended nutritional intake of 400 IU daily.

BONE MINERAL DENSITY

Bone mineral density and bone mineral content were measured in the lumbar spine and total body by means of dual energy x-ray absorptiometry (4500 densitometer; Hologic Inc, Bedford, Mass). Pediatric software was used in all pediatric patients, and they underwent testing at the same pediatric center (Shriner's Hospital, Montreal, Quebec). Adults (>18 years old) underwent BMD measurement (Lunar DPX; MEC Lunar Corp, Minster, Ohio).

Lumbar spine BMD was measured in all patients, and most patients underwent total body BMD measurement. Lumbar spine values were compared with age-appropriate, sex-appropriate, and height-appropriate standards developed at the Shriner's Hospital (Francis Glorieux, MD, oral communication, September 1996). For total body reference values, established sex-specific Canadian standards were used.⁶ If the patient was not within 2 SDs for age-appropriate height, data were corrected accordingly.⁷

STATISTICAL ANALYSIS

Data were analyzed by using Excel 1997 (Microsoft Corp, Redmond, Wash) and SPSS version 11 (SPSS Inc, Chicago, Ill). A 1-sided *t* test was used to compare mean lumbar spine and total body BMDs with those of the general population. Mean lumbar spine and total body BMDs were compared between the 3 groups by using analysis of variance. Lumbar spine and total body measurements for each patient were compared by using a paired *t* test. Multivariate analysis with forward stepwise regression with an F-to-enter value of 4 was performed to assess the effects of age, sex, calcium and vitamin D intake, activity level, and hormonal status on lumbar spine BMD.

ETHICS

Written informed consent was obtained from all participating patients and/or families. The study was approved by the institutional review board, Montreal Children's Hospital, McGill University Health Centre.

Table 1. Patient Characteristics*

Characteristic	All	Craniospinal Irradiation and Chemotherapy	Craniospinal Irradiation Only	Cranial Irradiation Only
No. of patients	24	8	11	5
Age at diagnosis, y	6.67 (2-14)	7.62 (3-14)	6.82 (3-14)	4.80 (2-9)
Age at study, y	12.08 (4-20)	11.50 (8-16)	13.64 (9-20)	9.60 (4-14)
M/F	11/13	2/6	5/6	4/1
Height z score	-0.84 (-3.24 to 0.99)	-1.02 (-1.97 to -0.14)	-1.26 (-3.24 to 0.68)	0.39 (-0.74 to 0.99)

*Unless otherwise indicated, the data are presented as mean (range).

Table 2. Risk Factors for Osteopenia

Risk Factor	All	Craniospinal Irradiation and Chemotherapy	Craniospinal Irradiation Only	Cranial Irradiation Only
Chemotherapy	8	8	0	0
Growth hormone deficiency, treated	11	5	5	1
Growth hormone deficiency, treatment refused	1	1	0	0
Hypothyroid, treated with L-thyroxine	9	3	6	0
Personal history of fractures	6	2	2	2
Family history of fractures	11	6	4	1
Smoking	1	0	1	0
Inhaled steroid use	1	0	1	0
Occasional alcohol use	4	1	2	2

RESULTS

Patients who had been treated with radiotherapy for posterior fossa tumors after 1987 were recruited from 1996 through 1999. Nineteen of a potential 29 patients with medulloblastoma were recruited (5 patients lost to follow-up, 5 deceased), and 5 of 6 patients with posterior fossa ependymoma were recruited (1 unwilling to participate).

Table 1 shows the general characteristics of the study patients. Eleven of the 24 patients were male. The mean age at tumor diagnosis was 6.67 years (range, 2-14). The patients underwent endocrinological examination a mean of 1.17 years after the diagnosis of brain tumor. The patients ranged in age from 4 to 20 years (mean \pm SD, 12.08 \pm 3.99 years) at the time of our study. Bone mineralization studies were performed a mean \pm SD of 5.42 \pm 3.23 years (range, 1-15) after therapy.

Potential risk factors for the development of osteopenia in our patients are listed in **Table 2**. All patients were previously healthy, with the diagnosis of brain tumor being their primary medical problem. Eleven of 12 patients who were growth hormone deficient (11 with medulloblastoma and 1 with ependymoma) received standard treatment (0.03 mg of growth hormone per kilogram of body weight per day, 6 days per week), and 1 refused treatment. All patients with biochemical hypothyroidism (primary in all cases) were treated with L-thyroxine. Six patients had a history of previous fractures; all were in keeping with the nature of the injury. Eleven of the 24 patients had a family history of fractures, without any family history of clinically important metabolic bone disease. Four female patients had hypogonadism; 3 had elevated follicle-stimulating hormone levels (>20 mIU/mL [IU/L]), and 1 had low luteinizing and follicle-stimulating hormone levels in the context of

a low estradiol level (<10 pg/mL [<37 pmol/L]), which suggested a central cause. One patient smoked, and 4 patients occasionally consumed alcohol. One patient used low-dose inhaled steroids.

No patient had any significantly abnormal laboratory values. No patient had grossly abnormal body proportions, which was screened by assessing arm span and upper-lower segment ratios, and only 1 patient had mild scoliosis. All patients except 1 had bone ages within 2 SDs of the mean for chronological age.

The children and young adults in our study had abnormally low BMD, with a mean total body BMD z score of -0.47 (95% confidence interval [CI], -0.85 to -0.09). Their lumbar spine BMD was also low, with a mean z score of -1.27 (95% CI, -1.81 to -0.73). The difference in lumbar spine BMD between the ependymoma (mean z score, -1.39 ; 95% CI, -2.95 to 0.17) and medulloblastoma (mean z score, -1.25 ; 95% CI, -1.83 to -0.67) groups was not significant. There was no significant difference in lumbar spine BMD between patients with medulloblastoma who underwent chemotherapy (mean z score, -1.18 ; 95% CI, -2.28 to -0.08), those who did not (mean z score, -1.29 ; 95% CI, -1.95 to -0.59), and those who had ependymoma (mean z score, -1.39 ; 95% CI, -2.95 to 0.17).

Seven patients underwent repeat measurements approximately 1 year later after supplementation with vitamin D and calcium. Five showed an increase in BMD, parallel to normal curves, without any compensatory increase, and BMD in 2 children remained static.

Our patients consumed a diet deficient in vitamin D (mean \pm SD, 53.6% \pm 24.1% of recommended nutritional intake) and calcium (mean \pm SD, 70.0% \pm 37.4% of DRI). Fifteen of 23 patients did not meet their DRI for calcium, and 19 of 23 did not meet their recommended nutritional intake for vitamin D. These deficiencies were

Table 3. Level of Activity

Activity Level	All Patients (N = 24)	Craniospinal Irradiation and Chemotherapy	Craniospinal Irradiation Only	Cranial Irradiation Only
Inactive	3	1	1	1
Moderately active*	15	5	8	2
Very active†	6	1	3	2

*Thirty minutes or more of activity at a time, 1 to 2 times per week.

†Thirty minutes or more of activity at a time, 3 or more times per week.

comparable between the groups: for the medulloblastoma group, mean calcium intake was 64.6% (95% CI, 47.8%-81.4%) of that recommended and mean vitamin D intake was 50.0% (95% CI, 38.4%-61.6%) of that recommended, and for the ependymoma group, mean calcium intake was 88.1% (95% CI, 47.3%-128.9%) of that recommended and mean vitamin D intake was 65.0% (95% CI, 46.6%-83.4%) of that recommended.

Table 3 shows the activity level of our patient population. Most (15 of 24) patients were moderately active (30 minutes or more of exercise 1 to 2 times per week), with 3 patients being inactive (2 patients did less than 30 minutes of exercise once per week, 1 patient was wheelchair bound) and 6 patients being very active (30 minutes or more of exercise 3 or more times per week). There was no significant difference in BMD between all 3 activity groups.

Four patients had primary hypothyroidism, 6 were growth hormone deficient, and 6 were both. There was no significant difference in lumbar spine BMD between patients who had no hormone deficiency vs those who had 1 or more deficiencies.

Six patients had a history of fractures, but all seemed appropriate in the context of the injury. There was no significant difference in lumbar spine BMD in patients with a history of fractures (mean *z* score, -1.56; 95% CI, -2.46 to -0.66) as compared with those with no history of fractures (mean *z* score, -1.18; 95% CI, -1.86 to -0.50).

Age was not associated with BMD. Analysis of variance was used to compare mean BMD for all Tanner stages, which did not reveal any significant differences.

Forward stepwise regression was performed to look at the effects of sex, age, hormone deficiencies (even if treated), gonadal dysfunction (treated), activity level, and calcium and vitamin D intake on lumbar spine BMD. The only variables that were found to have an effect on lumbar spine BMD, protective in both cases, were female sex and calcium intake. The regression coefficient for female sex was 1.422 (95% CI, 0.456-2.388) and for calcium intake was 0.015 (95% CI, 0.001-0.029).

COMMENT

Our data show that children and young adults who underwent irradiation for medulloblastoma or ependymoma have diminished BMD as compared with that of the general population. This reduction was found for both total body and lumbar spine measurements. Patients had similarly diminished BMD regardless of whether they had undergone only craniospinal irradiation, craniospinal ir-

radiation and standard chemotherapy, or only posterior fossa irradiation for ependymoma.

Our results support those of Mithal et al⁴ by showing that radiotherapy may cause osteopenia and that this osteopenia can occur outside of the radiation field. This finding is clearly shown in our patients with ependymoma, who, despite undergoing only posterior fossa irradiation, still had diminished BMD at the level of the lumbar spine. Mithal et al⁴ looked at only 7 adult patients who had undergone radiotherapy a mean of 28 years before the study. Contemporary irradiation techniques used in our patient group are more focused and have less scatter than those used 30 years ago and, therefore, more strongly support the idea that radiation-induced osteopenia may occur beyond the irradiation site. We and others speculate that radiation and the tumor itself may release cytokines and factors that affect bone remodeling and osteoblastic and osteoclastic activity.^{3,4,8,9}

Gilsanz et al³ studied 42 survivors of acute lymphoblastic leukemia and found that patients who had undergone cranial irradiation and chemotherapy had reduced BMD as compared with that of patients who had undergone only chemotherapy and age-matched control subjects. The authors of that study, like Mithal et al,⁴ speculated that radiation-induced growth hormone deficiency might have been responsible for the reduction in BMD. However, in both studies, formal growth hormone testing was not performed. In our study, the endocrinology service was involved early in the care of these patients and observed them closely. Any patients with reduced growth velocity underwent formal growth hormone testing. Twelve of 24 patients were deficient in growth hormone, but only 11 accepted therapy. Patients who were deficient in growth hormone had lumbar spine BMD comparable with that of the rest of the patients, and growth hormone deficiency was not found to be a contributor to reduced BMD.

Chemotherapeutic agents may cause osteopenia in children, although this question has been inadequately addressed in the pediatric population.¹⁰ Halton et al¹¹ showed that treatment regimens for acute lymphoblastic leukemia in which higher doses of prednisolone sodium phosphate and methotrexate sodium are used are associated with significant reduction in bone mineral content. On the other hand, in the study by Gilsanz et al,³ in which glucocorticoids were administered as part of an acute lymphoblastic leukemia treatment protocol, none of the patients who had undergone only chemotherapy had reduced BMD a mean of 3.7 years after therapy.

Our results confirm those of Gilsanz et al³ because our patients with medulloblastoma who had undergone chemotherapy and craniospinal irradiation had a similar, and not greater, reduction in BMD as compared with those who had undergone only craniospinal irradiation and the patients with ependymoma who had undergone only posterior fossa irradiation. This finding suggests that the particular chemotherapeutic regimen used in 1 subgroup of our patients (cisplatin, etoposide, vincristine sulfate, and cyclophosphamide) apparently does not contribute to osteopenia. Of note, however, cyclophosphamide, which results in gonadal failure, may increase the risk of osteoporosis in adults. Four of our 24 patients had hypogonadism and received appropriate treatment. Regression analysis revealed that hypogonadism, when treated promptly, was not a risk factor for osteopenia in our patients, which supports the idea that prompt diagnosis and treatment of gonadal failure may prevent osteopenia.

It is interesting that our patients had reduced total body and lumbar spine BMD but that the reduction of lumbar spine BMD was significantly greater than total body BMD regardless of radiotherapy target volume. The lumbar spine consists of trabecular bone, which has rapid turnover and so may be more sensitive to alterations in bone remodeling.^{12,13}

Our patient population had a diet deficient in vitamin D and calcium, with mean intake levels of both well below recommended amounts. Results of a study by Henderson et al¹⁴ of 60 survivors of childhood malignancies revealed that calcium intake correlated with BMD. Multivariate analysis demonstrated that calcium intake and female sex were the only variables associated with BMD, both being protective. We found a regression coefficient of 0.015 (95% CI, 0.001-0.029) for calcium intake, which translates into a 0.15 SD increase in the lumbar spine BMD z score for every 10% increase in calcium intake expressed as percentage of DRI. This observation remained constant across the range of calcium intake levels seen (-55% to +155% of DRI). Vitamin D was not a significant contributor in and of itself; however, because vitamin D intake often parallels calcium intake, it is likely a covariate.

The effect of female sex on lumbar spine BMD was striking. Our regression coefficient of 1.422 (95% CI, 0.456-2.388) indicates an increase in BMD z score by 1.4 in patients who are female. This result was not dependent on hormone replacement status or other regression variables. Arikoski et al,¹⁵ who looked at BMD in long-term survivors of acute lymphoblastic leukemia, also found that male sex was associated with lower lumbar and femoral BMD. In contrast, authors of 1 study of BMC and BMD in healthy children found reduced BMD in girls as compared with that in boys.¹⁶

Seven children had repeat BMD measurements 1 year later after supplementation with vitamin D and calcium to reach the recommended intake levels. Five of these 7 patients had an increase in BMD parallel to normal curves but did not show any compensatory increase.

In summary, our patients had a reduction in both lumbar spine and total body BMD. This reduction was similar within all 3 treatment groups, which suggests that

Childhood is an important time for skeletal growth and deposition of bone mass. Children with certain brain tumors undergo craniospinal irradiation as part of their treatment regimen. Results of some reports suggest that irradiation of the brain may cause diminished BMD. Results of reports in adults suggest that this osteopenia may occur at sites distant from the irradiated area.

In this study, we found diminished BMD in children who had undergone cranial or craniospinal irradiation. This osteopenia was detected at sites outside the radiotherapy field. Chemotherapy did not seem to play a significant role. Increased calcium intake was found to be protective, and children who received calcium supplementation had an increase in BMD 1 year later. Supplementation with calcium before irradiation may prevent osteopenia, so prospective studies of this potential are warranted.

chemotherapy did not play a role and that localized irradiation may have systemic effects. The only factors that were significant contributors were female sex and calcium intake. Of the small subset of patients we evaluated longitudinally, none had any compensatory increase.

One hypothesis as to why these children developed osteopenia and were not capable of improving their BMD after radiotherapy is that radiotherapy may cause an acute loss of BMD. The exact mechanism of this radiation-induced osteopenia is yet to be elucidated but appears not to be linked to disturbances in the "usual" hormones—growth hormone, thyroid hormone, and sex steroids. Children who met their recommended intake levels of calcium and vitamin D remained more or less in the normal BMD range after insult as compared with those with deficient intake levels who had the lowest BMD at the time of our study. This hypothesis suggests that supplemental calcium and vitamin D may be an important modifiable factor as long as calciuria is monitored. Patients with posterior fossa brain tumors often have balance problems and gait disturbances that may persist after therapy. This increased risk of falling, coupled with a reduction in bone density, may place these patients at considerable risk of fractures.

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Announcement

Papers From Symposium on Cochlear Implants in Children Published in May 2004 *Archives of Otolaryngology-Head & Neck Surgery*

The May 2004 issue of *Archives of Otolaryngology-Head & Neck Surgery* features papers from the Ninth Symposium on Cochlear Implants in Children, held in Washington, DC, in April 2003. Sponsored by the Listening Center at Johns Hopkins and the River School of Washington, DC, the symposium served as an international forum for issues related to early-onset deafness and its rehabilitation. Advances in early diagnosis of deafness now allow the process of hearing rehabilitation to begin before the age of 3 months; combined with technological improvements in multiple channel implants, this carries clear implications for the safety of early implantation and the services that allow children to use this technology to its fullest.