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Original Paper

Osteopenia in Children Surviving Brain Tumours

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Osteopenia has been reported in children surviving acute lymphoblastic leukaemia, apparently as a consequence of therapy. It has been suggested that cranial irradiation may play a crucial role in this disorder. To explore that possibility, survivors of brain tumours in childhood, all of whom had received radiotherapy, were examined for evidence of bone mineral loss. 19 children were assessed, on average at 7 years after treatment. Measurements of growth velocities, plain radiography of the skeleton, bone densitometry, health-related quality of life and physical activity were undertaken. Growth hormone (GH) deficiency had been detected in 6 children and 5 had received GH replacement, for a minimum of more than 3 years. 9 children were radiographically osteopenic (including the 5 who had received GH). *Z* scores for bone mineral density (BMD) were negative in the majority of children. Health-related quality of life was less and pain more frequent in those with low BMD scores. Pain was correlated negatively with both free-time activity and seasonal activity ($P < 0.01$). Osteopenia is a common sequel of therapy in children with brain tumours. Those with osteopenia have more pain and more compromised, health-related quality of life than those who are not osteopenic, and pain significantly limits physical activity. The pathogenesis of osteopenia in these children is still uncertain, but is likely to be multifactorial.

Key words: osteopenia, children, brain tumours
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INTRODUCTION

AMONG THE many short- and long-term consequences of otherwise increasingly successful treatment of cancer in children is musculo-skeletal morbidity [1]. In the commonest form of malignant disease in childhood (acute lymphoblastic leukaemia (ALL)), pain is reported in 45–70% of patients during therapy [2, 3], apparently related, at least in part, to osteopenia which is associated with disturbances of gait and frequent fractures [4]. These prevalent sequelae can persist long after treatment has been completed [5, 6]. Effective management and ultimate prevention of this disorder will depend on identification of causal factors and an understanding of the pathogenesis.

In previous investigations, we have described this clinical circumstance in detail and have deduced that corticosteroid therapy plays an important aetiological role [7]. Others have postulated that cranial irradiation is implicated, perhaps by the mechanism of growth hormone (GH) deficiency [8, 9]. However, in contrast to osteopenia, GH deficiency is uncommon after treatment for ALL, especially with the ever more limited use of radiotherapy [10], the administration of progressively lower doses of whole brain radiation (now usually 18 Gy) [11] and, potentially, with the lower toxicity associated with hyperfractionation schedules [12].

Our recent preliminary studies suggest that cranial irradiation is not a significant causal factor in osteopenia, at least in children with ALL [13]. Nevertheless, in order to explore such a possible association further, we examined children who survived brain tumours and who received doses of cranial irradiation higher than those administered to patients with ALL. Resolving the pathogenesis of osteopenia in children with cancer has obvious implications for the design of future treatment strategies, both antineoplastic and rehabilitative.

PATIENTS AND METHODS

All children who had been treated for brain tumours in Hamilton, Canada were eligible if they had received radiotherapy, had completed all treatment approximately 1 year or

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more prior to this investigation, and were currently ambulant. In addition to demographic information, details of treatment were obtained by review of records. Informed consent was obtained from the children's parents and the study protocol was approved by the Research Advisory Group of McMaster University's Faculty of Health Sciences.

The components of this cross-sectional study were: determination of current height and weight, so allowing the calculation of growth velocities according to the normative standards of Tanner and colleagues [14, 15]; an assessment of osteopenia (present or absent) by a single observer (GJG) using plain antero-posterior radiographs of the hips, knees, ankles and wrists. This is a demonstrably reliable and sensitive estimate [16]; measurement of bone mineral density (BMD) of the lumbar vertebrae and femoral necks using a Hologic 4500A (X-ray based) bone densitometer (Hologic Inc., Waltham, Massachusetts, U.S.A.). Bone mineral measurements were compared with normative standards established for children elsewhere in Canada [17], using equipment from the same manufacturer. Comparison of the BMD with the reference population was computed as a deviation or *Z* score to allow comparison across age and gender; a parental assessment of each child's global health status and health-related quality of life (HRQL) using a 15-item questionnaire derived from the multi-attribute Health Utilities Index Mark 2 (HUI2) and Mark 3 (HUI3) [18], with calculations of corresponding utility scores afforded by this preference-linked approach [19]; and an assessment of each child's physical activity during the last year using a 61-item questionnaire, with established reliability, from which summary scores were calculated [20]. In almost half the instances, this was completed by the child.

Statistical analyses were performed by linear regression and the Wilcoxon test for two samples.

Table 1. *Patients' diagnoses and radiotherapy*

Patient no.	Diagnosis	Treatment volumes (cm) RL	LL	PO/AO	Dose (Gray)	Fraction number	Time (weeks)
	Cerebellar astrocytomas						
1		7.5×8	7.5×8	7.5×8	50	30	6
2		13×10	13×10	—	45	29	6
3		9.5×9.5	9.5×9.5	—	50	30	6
4		9×8.5	9×8.5	—	54	30	6
	Other grade (1/2) astrocytomas						
5	Pineal	7×6.5	7×6.5	7×6.5	55	35	7
6	Hypothalamic	9.5×9	9.5×9	9×9	50	33	6.5
7	Suprasellar	10×7.6	10×7.6	8.5×7.6	50	30	6
8	Suprasellar	5.5×6.8	5.5×6.8	5.5×6.8	50	30	6
9	Brain stem	8.5×8	8.5×8	7×8	55	35	7
10	Brain stem	10×7.6	9.5×9	9×9	50	30	6
	Grade (3/4) astrocytomas						
11	Parieto-occipital	20×15	20×15	—	38.5	22	4.5
		Boost	12×10.2	(9.5×10.5)×2	13.6	8	1.5
12	Cerebellar	—	10×9.5	8.5×9.5*	54	30	6
	PNET						
13	Posterior fossa	21.5×20	21.5×20	Brain	35	20	4
		5.5×28.5		Spine	35	20	4
		10.5×8.5	10.5×8.5	Boost	20	12	2.5
14	Posterior fossa	21×18.5	21×18.5	Brain	35	23	4
		5.5×28.5		Spine	35	25	5
		10.5×8.5	10.5×8.5	Boost	20	12	2.5
15	Frontal	18×15	18×15	Brain	30	20	4
		5.6×35.3		Spine	30	20	4
		10.5×13	10.5×13	Boost	20	12	2.5
16	Temporal	19×17.5	19×17.5	Brain	50	50†	5
		6.5×38.5		Spine	40	44†	4.5
		18×8	18×8	Boost	15	15†	1.5
17	Parieto-occipital	14.8×19	14.8×19	Brain	30	21	4
		4×31.5		Spine	30	25	5
		13×13.5	13×13.5	Boost	17.5	12	2.5
	Ependymoma						
18	Cerebellar	12.5×15	12.5×15	—	51.4	31	6
19	Lumbosacral	19×20	19×20	Brain	30	20	4
		8.2×36.4		Spine	40	28	5.5
		8.2×19.2		Boost	10	7	1.5

RL, right lateral; LL, left lateral, PO/AO, posterior or anterior oblique; PNET, primitive neuro-ectodermal tumour (medulloblastoma).
*Posterior wedged. †Hyperfractionation.

RESULTS

Patient population

30 children fulfilled the eligibility criteria, but 1 died before study, 3 were lost to follow-up, 6 declined to participate and 1 underwent technically flawed densitometry. The study group therefore consisted of 19 subjects (5 males and 14 females).

Disease and treatment data

4 children had low grade cerebellar astrocytomas, 6 had other grade (1/2) astrocytomas, 2 had high grade (3/4) astrocytomas, 5 had primitive neuro-ectodermal tumours (medulloblastomas), and 2 had ependymomas (Table 1). All underwent surgical resection, which in 9 was grossly complete. In each case, the tumour volume received at least 40 Gy and the hypothalamus/pituitary was judged as having been irradiated in 12 cases. 6 children received adjuvant chemotherapy which, in 2 instances, included corticosteroids. An additional 5 children had been given steroid therapy for symptomatic control.

Age distributions

The ages at diagnosis, conclusion of therapy and current investigation are given in Table 2, together with the corresponding intervals. The average age at diagnosis was approximately 7 years (and 2–6 months older at the end of treatment), and almost double that at the time of the current investigation, when only 3 children were still prepubertal.

Height and weight

The centiles for height ranged from 1 to 100 (mean 49, median 70) and for weight from 3 to 100 (mean 58, median 67). All but 6 children had sustained growth velocities above the third centiles. Only this group of 6 were tested formally for GH deficiency (which was confirmed in all of them). 5 of the 6 received GH replacement therapy—the other child declined (and manifest precocious puberty). Of these 5 children, 3 had completed GH replacement having received therapy for 4 years 10 months, 5 years and 5 years 6 months. Both of the other children had been receiving GH replacement for 3 years and 5 months when they entered this study.

Radiographic assessment

While blinded to the results of bone densitometry, the experienced observer categorised 9 children as osteopenic and 10 as not. There were no significant differences between these groups with respect to centiles for height or weight, or the ages or time intervals in Table 2. All GH deficient children were osteopenic.

BMD

In the lumbar spine, the Z scores ranged from -2.91 to $+1.15$ (median -1.05, mean -0.98). 16 of 19 children (84%) had negative Z scores. In the femoral necks, the Z scores ranged from -2.38 to $+2.38$ (median -0.84, mean -0.64). 14 children had negative Z scores. The relationships between radiographic assessments of osteopenia and measurements of BMD are listed in Table 3. There were no significant correlations between the Z scores for vertebrae or femora and centiles for height or weight, nor between these Z scores and any of the ages or time intervals in Table 2 (data not shown). Furthermore, there was no significant difference between the Z scores in the lumbar spine for those who had undergone spinal irradiation ($n=6$, mean $=-0.98$, median $=-1.24$) and the Z scores for those who had not ($n=13$, mean $=-0.98$, median $=-1.03$).

In the GH deficient children, all but one of whom had had replacement therapy, the mean Z scores for vertebrae and femora were -1.13 and -1.45, respectively. The corresponding scores for non-GH deficient children were -0.45 and -0.76. These differences were not statistically significant. Therefore, it is not surprising that there were no significant differences in the Z scores between children who were judged to have received hypothalamic/pituitary irradiation and those who were not (data not shown). However, it must be acknowledged that there is the prospect of a type II error, as the power to detect a true difference between samples of this size is low.

Again, there were no statistically significant differences in Z scores between children who had received steroids and those who had not; reflecting the low doses and short duration of therapy, by comparison with the experience of children with ALL, and the long average interval between treatment and testing.

Assessments of global health status and HRQL

As determined in the HUI3 system, all but 2 of the children were without compromise in ambulation, so confirming their eligibility for this study on the basis of that criterion. The utility scores for global health status, as measures of HRQL, ranged from 0.59 to 1.00 (median 0.90, mean 0.85) on a 0.00 to 1.00 scale from death to perfect health. The correlation between these scores and BMD values was statistically significant ($r=0.46$, $P<0.05$) for the femora but not the vertebrae. In a single attribute analysis, 10 of 19 parents reported pain in their children using the HUI2 system and 8 of 19 with the HUI3 system. In each comparison (Table 4), children in whom pain was reported had median BMD values lower than those who did not experience pain, although in

Table 2. Age distribution of the study population (months)

	A	B	C	D	E
Range	18–154	23–184	66–214	13–129	11–126
Median	87	89	160	81	77
Mean	82	88	167	75	69

A, age at diagnosis; B, age at conclusion of therapy; C, age at current investigation; D, interval from A to C; E, interval from B to C.

Table 3. Radiographic assessments and densitometric measurements

	Z scores	
	Lumbar vertebrae	Femoral necks
Osteopenia present*		
Range	-2.55 to $+0.12$	-2.38 to $+2.38$
Median	-1.72	-1.34
Mean	-1.47	-0.86
Osteopenia absent*		
Range	-2.91 to $+1.15$	-1.93 to $+1.35$
Median	-0.38	-0.48
Mean	-0.53	-0.44
P value†	<0.05	n.s.

*As judged radiographically. †Difference between osteopenic and non-osteopenic. n.s., not significant.

Table 4. A comparison of the presence or absence of pain and bone mineral density

	Z scores	
	Femora	Vertebrae
HUI2		
Pain (Yes)		
Range	− 2.38 to − 0.27	− 2.14 to + 1.15
Median	− 1.34*	− 1.24
Mean	− 1.34*	− 0.91
Pain (No)		
Range	− 2.23 to + 2.38	− 2.91 to + 0.12
Median	− 0.19	− 0.51
Mean	+ 0.06	− 1.05
HUI3		
Pain (Yes)		
Range	− 2.38 to − 0.27	− 1.90 to + 0.91
Median	− 1.31	− 1.24
Mean	− 1.20	− 0.78
Pain (No)		
Range	− 2.23 to + 2.38	− 2.91 to + 1.15
Median	− 0.19	− 1.05
Mean	− 0.19	− 1.23

*No pain versus pain, $P < 0.025$.

only one instance (femoral BMD values in the HUI2 system) did this achieve formal statistical significance.

Activity levels in organised sports, free-time activity and seasonal activity

The scores are displayed in Table 5. There were no significant correlations between any of the activity scores and BMD *Z* scores, nor between activity scores and utility scores (as measures of global HRQL). However, there were statistically significant negative correlations between the levels on the pain attribute in HUI3 and free-time activity ($r = 0.59$, $P < 0.01$), as well as seasonal activity ($r = -0.63$, $P < 0.01$).

DISCUSSION

The issue addressed in this report is not whether osteopenia in children can be the result of GH deficiency, for the evidence on that issue is strong [21]. Rather the question to answer is that of the basis for osteopenia in children who are engaged in active therapy for cancer and in those who have completed treatment for these diseases, for osteopenia is a common form of early and late morbidity in such children [7] so demanding attention for treatment and prevention.

Points against a prominent causal role for GH deficiency in osteopenia occurring in children who had ALL include: the low frequency of GH deficiency in contrast to the high prevalence of osteopenia in such children [10]; the lack of a significant difference, in either the prevalence or severity of osteopenia, between children who underwent cranial irradiation and those who did not [13]; and the progressive rise in serum osteocalcin levels during treatment, accompanied by at least normal concentrations of type 1 collagen cross-linked N telopeptide in the urine [7], for these measures, respectively, of bone formation and resorption, are typically low in the context of GH deficiency [22–27].

In children who have survived brain tumours, similar arguments can be advanced on the basis of the present study. For example, there was no significantly greater frequency or severity of osteopenia (as judged by BMD values) in those who were demonstrably GH deficient than in those who were not. Moreover, those children who had received or who were receiving GH replacement were still osteopenic and the single GH deficient child who refused replacement therapy was the only one who was not osteopenic (but he had experienced precocious puberty). Although there may be an initial fall in BMD after the start of GH replacement therapy [28, 29], the patients in the present study were long past such a phase of response, and recovery of BMD may continue after administration of GH has ceased [30, 31]. However, it is recognised that the present results are subject to a type II error and an expanded sample size will be required to address this issue definitively.

Table 5. Activity scores

	Organised sports*	Free-time activity*	Seasonal activity*
Range	0–21	1–13	3–13
Median	1	8	7
Mean	3	7	8
Normal†	7.51 ± 4.34	7.85 ± 2.25	14.02 ± 2.58

*Possible ranges for scores are: organised sports 0–30; free-time activity 0–14; and seasonal activity 0–20. †Derived from a sample of 576 children age 8–14 years [19].

Nevertheless, whether judged radiographically or measured by BMD, osteopenia was prevalent among these children who had survived brain tumours. The clinical importance of this observation is reflected in its relationship to global health status, in part at least as a consequence of associated pain (of variable location) which, in turn, significantly limits physical activity. Specifically, although the children in this study engaged in as much free-time activity as normal children, they participated much less in organised sports and seasonal activities. Similar results have been reported by others [32]. Perhaps this reflects an additional element of parental protection. The markedly different activity profile in these children, compared with normal children, may have long-term consequences for their health.

Evidently, the natural history of this disorder (osteopenia) and its accompanying burden of morbidity will become clear only with longitudinal studies of such patients. In a cross-sectional study of very long-term survivors of ALL in childhood (average duration of follow-up more than 10 years) who had received several different treatment regimens, it has been reported that osteopenia was no more prevalent than expected [33]. Our own experience, in a longitudinal study, does suggest that resolution may follow the completion of therapy, at least in those who do not receive cranial irradiation [13]. Support for such an evolution comes from the recent description of the preliminary observations of other investigators [34]. However, in a cross-sectional study of long-term survivors of ALL in childhood (average duration of follow-up more than 6 years) [6], almost all of whom had received cranial irradiation, osteopenia was prominent.

It may be that loss of bone mineral mass can be a consequence of more than one insult in children with cancer. Steroid therapy is an obvious candidate and cranial irradiation may play a role, but by a mechanism not yet defined.

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