
ORIGINAL ARTICLE

Effect of Cranial Irradiation on Pituitary Size in Patients Cured of Acute Lymphoblastic Leukaemia: Retrospective Study

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ABSTRACT

Objective: To evaluate the pituitary glands of patients previously treated for acute lymphoblastic leukaemia with cranial irradiation.

Patients and Methods: Thirty nine patients who were cured of acute lymphoblastic leukaemia and who were regularly followed up from 1979 to 1992 were recruited. Sagittal T1-weighted magnetic resonance imaging of the pituitary gland was performed in a 1.5-T magnetic resonance machine. Sixteen age- and sex-matched patients who had been treated during childhood for solid extracranial neoplasms with systemic chemotherapy, but not intracranial irradiation, were recruited as controls.

Results: The height of the adenohypophysis was significantly smaller in patients who had had acute lymphoblastic leukaemia (mean, 3.9 mm; standard deviation, 1.2 mm) than in control patients (mean, 5.3 mm; standard deviation, 1.1 mm) [$p < 0.001$]. For both patients who had had acute lymphoblastic leukaemia and for controls, there was no significant correlation between pituitary height and age at diagnosis or age at the time of the study. In the group of patients who had had acute lymphoblastic leukaemia, the pituitary was shorter in those treated with more than 18 Gy of radiation (mean, 3.0 mm; standard deviation, 1.3 mm) than in those treated with exactly 18 Gy (mean, 4.1 mm; standard deviation, 1.1 mm) [$p = 0.037$].

Conclusion: Children cured of acute lymphoblastic leukaemia with previous cranial irradiation show a significant reduction in the height of the adenohypophysis. The effect on the size of the pituitary gland appears greater with a higher radiation dose.

Key Words: Cranial irradiation; Leukemia, lymphocytic, acute/radiotherapy; Pituitary gland/radiation effects

INTRODUCTION

Acute lymphoblastic leukaemia (ALL) is the most common malignancy of childhood.¹ Neurological complications are common, both during and after the completion of therapy. The endocrine system is also particularly sensitive to cancer therapies and the long-term effects that radiotherapy and chemotherapy have on the endocrine system are becoming increasingly recognised.² One notable example is the damaging effect to the

hypothalamo-pituitary axis.²⁻⁴ Some 65% of children with ALL treated with 20 to 30 Gy of cranial radiation have impaired serum growth hormone responses to provocative stimulation.⁴ In addition, Paakko et al⁵ evaluated 29 survivors of a multitude of childhood cancers who had received radiation therapy to the hypothalamo-pituitary axis (doses ranging from 10 to 46 Gy) and observed a shortened pituitary gland in midline sagittal magnetic resonance images when compared with age- and sex-matched controls. However, the heterogeneous nature of the tumours studied and their rather varied treatment methods, which included surgery in some and focal irradiation in the others, introduced different confounding factors. The main purpose of this study was to evaluate pituitary glands more specifically in Chinese survivors of ALL who had received whole-brain, but not focal, irradiation for central nervous system (CNS) prophylaxis.

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PATIENTS AND METHODS

Patients were recruited from the Children's Cancer Centre database of the Prince of Wales Hospital. Patients were eligible for study participation if they had had ALL and had survived more than 5 years from diagnosis; patients who had experienced a relapse were excluded from the investigation. Clinical information concerning treatment dates and protocols was obtained by reviewing medical records. All patients had received chemotherapy followed by cranial irradiation and chemotherapy as prophylaxis. Patients who had been treated during childhood for solid extracranial neoplasms using systemic chemotherapy, but not intrathecal therapy or cranial irradiation, were recruited as controls. The study and control groups were age- and sex-matched because both age and sex are significant factors affecting pituitary size.⁶⁻¹⁰ Informed consent was obtained from patients or their guardians. The study was approved by the local institutional ethics committee.

Magnetic resonance imaging (MRI) was performed on all patients at 1.5 T (Gyrosan NT; Philips Medical Systems, Best, Netherlands), using T1-weighted sagittal spin echo (repetition time, 500 ms; echo time, 15 ms; slice thickness, 5 mm; 256 x 256 matrix; excitation number, 2; and field of view, 230 mm). The midline sagittal image was used to assess the size of the pituitary gland. The longest measurement perpendicular to the maximum anteroposterior diameter of the pituitary gland was taken as the height of the adenohypophysis.⁵ The simple index of pituitary height was chosen for this study because pituitary gland height on sagittal images provides a good single measure for the assessment of pituitary gland size when with volume measurement.⁶

Student's *t* test was used to compare the mean size of the pituitary gland (and other characteristics) of the ALL group with that of the control group, and to compare the mean size of the pituitary gland in the patient subgroup that received prophylactic radiation at 18.0 Gy (the usual prophylactic dose for paediatric patients at our institution) and the subgroup that received more than 18.0 Gy. A *p* value of less than 0.05 was regarded as statistically significant.

RESULTS

A total of 39 patients who were treated at our centre between 1979 and 1992, and who had ALL diagnosed more than 5 years previously agreed to take part in this study. They had been treated with cranial irradiation (of at least 18 Gy) and intrathecal methotrexate, as well

as systemic chemotherapy according to various protocols. Sixteen control patients were recruited; they had been treated with various chemotherapy protocols for Wilms' tumour (*n* = 2), Hodgkin's disease (*n* = 3), osteosarcoma (*n* = 2), Langerhans' cell histiocytosis (*n* = 1), rhabdomyosarcoma (*n* = 3), neuroblastoma (*n* = 1), Ewing's sarcoma (*n* = 2), chronic myeloid leukemia (*n* = 1), and ovarian sex cord tumour (*n* = 1). None of the controls had been treated with intrathecal chemotherapy or cranial irradiation. The 2 groups were similar with respect to sex and age at MRI examination and diagnosis, although the mean interval from diagnosis was longer for the patients with ALL (Figure 1 and Table 1).

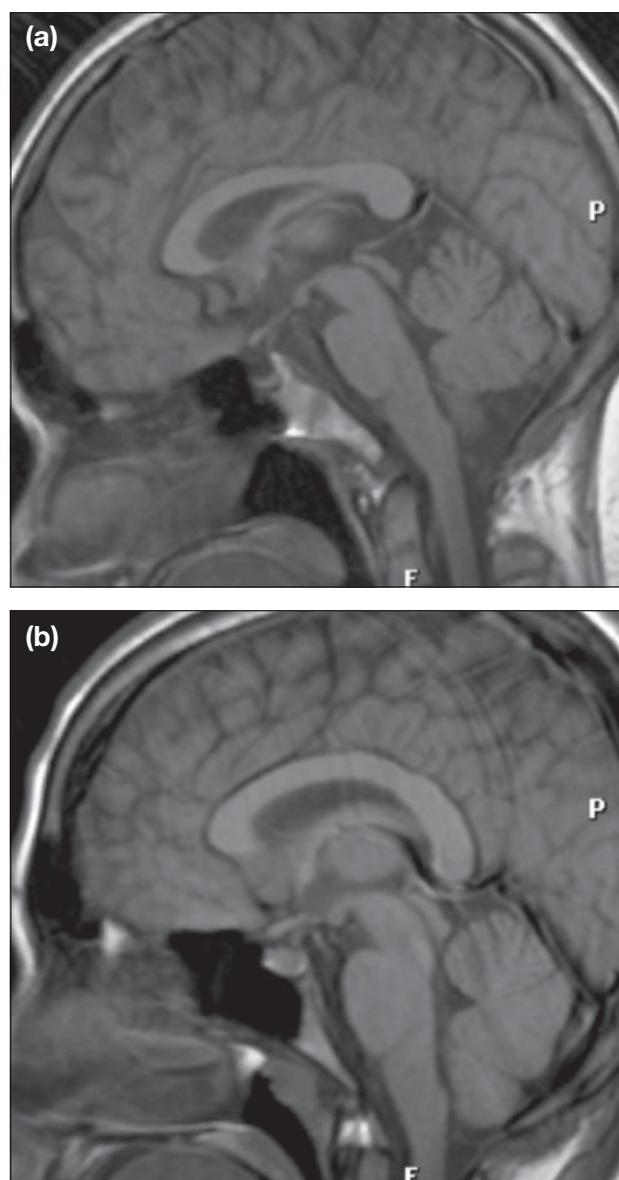


Figure 1. Sagittal magnetic resonance images of (a) a patient with acute lymphoblastic leukaemia and (b) a control patient. (P = occipital lobe and F = C2).

Table 1. Clinical characteristics of patients with acute lymphoblastic leukaemia (ALL) and control patients.

| Characteristic | Patients with ALL | Control patients | p Value |
|-----------------------------|-------------------|------------------|---------|
| No. | 39 | 16 | na |
| No. of males (%) | 27 (69) | 11 (69) | |
| Age at examination (y) | | | |
| Mean (SD) | 18.0 (3.9) | 16 (3.3) | ns |
| Range | 12-27 | 12-25 | na |
| Age at diagnosis (y) | | | |
| Mean (SD) | 5.1 (2.8) | 6.8 (3.5) | ns |
| Range | 0.83-13.7 | 1.3-13.0 | na |
| Interval from diagnosis (y) | | | |
| Mean (SD) | 12.7 (3.2) | 9.3 (3.6) | 0.002 |
| Range | 5-19 | 5-16 | na |

Abbreviations: na = not applicable; ns = not significant.

The height of the adenohypophysis in the study group ranged from 1.4 mm to 6.0 mm and the mean was 3.9 mm (standard deviation [SD], 1.2 mm). For the control group, the height of the adenohypophysis ranged from 3.4 mm to 6.9 mm and the mean was 5.3 mm (SD, 1.1 mm). The adenohypophysis height was significantly smaller among patients who had had ALL than among the control patients ($p < 0.001$). For both the study and control groups, there was no significant correlation between pituitary height and age at diagnosis or age at the time of the MRI study. The mean time since diagnosis was significantly longer in the ALL group than in the control group (12.7 years [SD, 3.2 years] vs 9.3 years [3.6 years]; $p = 0.002$).

Among the patients who had had ALL, 32 received 18.0 Gy of irradiation as cranial prophylaxis and 7 patients received more than 18.0 Gy (range, 22.8-36.0 Gy; mean, 25.7 Gy). These 7 patients were all males aged 17 to 27 years (mean, 21 years) at the time of the MRI examination. The mean height of their pituitary glands was significantly lower than that of patients treated with exactly 18.0 Gy of irradiation (3.0 mm [SD, 1.3 mm] vs 4.1 mm [SD, 1.1 mm]; $p = 0.037$). The mean pituitary height of the 32 patients who had had ALL who were treated with 18.0 Gy was significantly smaller than the mean pituitary height of controls (4.1 mm [SD, 1.1 mm] vs 5.3 mm [SD, 1.1 mm]; $p < 0.001$).

DISCUSSION

Overall long-term survival among patients with ALL is about 70%, although for individual patients, survival varies from about 40% to 90%, depending on prognostic features at diagnosis and early response to therapy. CNS relapse, however, formerly occurred in 50% or more of patients.¹¹⁻¹³ This phenomenon led to the introduction of CNS prophylaxis for children with ALL.

The most commonly used method in the 1970s and 1980s involved cranial irradiation — originally to a dose of 24 Gy, but later to 18 Gy¹⁴ — and intrathecal chemotherapy with methotrexate. This regimen reduces the rate of isolated CNS relapse to 5% to 10%,^{11,15,16} but it is associated with various forms of damage to the hypothalamo-pituitary axis.

Because the pituitary gland has no brain barrier, the pituitary parenchyma would be exposed to the effect of intravenous chemotherapy. By recruiting controls with cancer treated with intravenous chemotherapy, the confounding effect of systemic upset due to the presence of cancer and exposure to chemotherapy would be reduced, if not eliminated. In this way, the pituitary changes in survivors of ALL should reflect predominantly the effect of cranial irradiation. Ideally, patients who have received cranial irradiation but not chemotherapy would be the most suitable participants for the study group, but there are few such cancer patients, and they also tend to have undergone surgical treatment or focal irradiation.

The height of the pituitary gland correlates well with pituitary volume⁶ and function, as measured by spontaneous nocturnal growth hormone secretion,⁷ which is widely used to assess the pituitary size.⁷⁻¹⁰ In our study, the mean pituitary height in survivors of ALL (3.9 mm) was significantly smaller than in controls (5.3 mm).

Within the group of patients who had had ALL, the height of the pituitary was smaller in those treated with more than 18.0 Gy of irradiation (mean, 3.0 mm) than in those treated with exactly 18.0 Gy (mean, 4.1 mm). Nonetheless, with even 18.0 Gy of irradiation, the pituitary height remained significantly smaller than that in controls, which concurs with the findings of Melin et al,¹⁷ who showed that growth hormone deficiency is still common even after a reduction in dose from 24 Gy to 18 Gy in children irradiated for ALL. Growth hormone deficiency and premature sexual development have been shown to occur following fractionated radiation of doses of as low as 18 Gy, and they constitute the most common neuroendocrine problems encountered among irradiated children.¹⁸ In contrast, cranial irradiation with 18 Gy does not seem to influence the growth pattern of most children who are treated for ALL, despite severe impairment of growth hormone secretion and morphological abnormalities of the sellar area.¹⁹

The mechanism of radiation damage to the hypothalamic-pituitary axis is not known. It probably includes direct injury to the cells responsible for hormonal secretion, injury to the stroma or its microvasculature, or injury to the vascular channels that transfer the hypothalamic hormones to the pituitary.³

In summary, our results are consistent with published evidence of a reduction in pituitary height after cranial irradiation during childhood.^{5,19} Greater susceptibility to hypothalamo-pituitary irradiation has been reported in younger children with ALL.¹⁵ We did not, however, confirm the correlation between age at diagnosis and pituitary height that was reported by Cicognani et al.¹⁹

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