Cognitive function after two doses of cranial irradiation for acute lymphoblastic leukaemia

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Abstract

The cognitive function of 23 children given cranial irradiation in a dose of 24 Gy was compared with that of 41 given 18 Gy. No significant differences were found in intellectual function or in mean number of intelligence quotient points lost between patients in the two treatment groups. A reduction in the dose of cranial irradiation does not seem to alleviate long term neuropsychological deficits.

The philosophy of management of childhood malignancy has changed from one of cure at 'almost any cost' to one of 'cure at least cost'. This is exemplified by the treatment of acute lymphoblastic leukaemia in which increasing long term survival brought an awareness of neuropsychological deficits. The cranial irradiation given to treat occult disease of the central nervous system was regarded as the most likely cause of the observed cognitive problems. Because of this the dose of cranial irradiation given to most children in the United Kingdom was reduced in the mid 1980s from 24 Gy to 18 Gy. A previous study in Newcastle showed clear deficits in intellectual function in children with acute lymphoblastic leukaemia treated with 24 Gy when compared both with sibling controls and with children treated for solid tumours who had not received cranial irradiation.¹ A follow up of this initial cohort showed that the deficits persisted.² The same methods have now been applied to a group of children with acute lymphoblastic leukaemia treated with 18 Gy, and a comparison made with the original children treated with the higher dose of irradiation.

Patients and methods

Twenty three children (14 boys and nine girls) treated with 24 Gy and 41 (20 boys and 21 girls) treated with 18 Gy were studied, together with one sibling control for each. Their ages at diagnosis and at time of testing are shown in table 1.

Each child was given the four British Ability Scale subtests appropriate to their age.³ All

Table 2 Mean (SD) IQ before and after treatment and points lost in the two groups

	Irradiation dose	
	24 Gy (n=23)	18 Gy (n=41)
Estimate before treatment	104.3 (4.4)	105.2 (8.8)
After treatment	99.1 (13.2)	100.9 (15.4)
Points lost	5.2 (12.4)	4.3 (12.5)

received the similarities test (verbal reasoning), the matrices test (abstract reasoning), and the recall of digits test (immediate memory). Those over the age of 8 years were also given the speed of information processing test and those less than 8 were given the naming vocabulary test (retrieval and application of knowledge). A pretreatment estimate of intelligence quotient (IQ) was derived using a method described by McNemar,⁴ by which the patient is deemed to have an IQ halfway between the sibling's score and 100—for example, the pretreatment estimate for a child whose sibling scores 130 is 115, and if the sibling scored 90 the pretreatment estimate would be 95.

Results

The results of the full scale IQ assessment are shown in table 2, together with estimates before treatment that were derived from the sibling scores. The mean (SD) loss of IQ in the 24 Gy group was 5.2 (12.4) and in the 18 Gy group 4.3 (12.5). Student's *t* test showed that there was no significant difference between the two groups in the number of IQ points lost.

The *t* test also showed no significant difference in IQ scores between the two groups, and no significant differences in the shape of the profiles calculated for the individual subtests that comprised the IQ measurements in the two groups. A paired *t* test, however, showed that patients in both groups had IQ ratings significantly below those of their calculated estimates before treatment (24 Gy: $p < 0.05$, 18 Gy: $p < 0.01$).

Discussion

These results indicate that children treated with 18 Gy have deficits that are almost identical to those identified earlier in the 24 Gy group. The reduction in the dose of radiation does not seem to have affected the degree of deficit. Two possible reasons for this could be that there has not been sufficient reduction in dose, or that the deficits are not caused by the irradiation. Several centres in the United States have been

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Accepted 23 May 1991

(Arch Dis Child 1991;66:1245-6)

Table 1 Age of children at time of diagnosis and testing (months)

Irradiation dose	Age at diagnosis		Age at test	
	Mean (SD)	Range	Mean (SD)	Range
24 Gy (n=23)	48.5 (24.1)	16-105	119 (25.8)	88-182
18 Gy (n=41)	56.0 (36.0)	10-162	118.5 (37.0)	55-253

attempting to treat children without irradiation, but giving instead high doses of parenteral and intrathecal methotrexate to treat the occult disease of the central nervous system. Some recent studies have suggested that identical intellectual deficits may also be seen in these children suggesting either that the methotrexate causes similar problems to irradiation, or that intellectual damage might be caused by the disease itself.

There is no unanimity, however, in the reports of intellectual deficits in children with acute lymphoblastic leukaemia. Meadows *et al* were unable to show the same intellectual deficits in children treated with 18 Gy as they had described with 24 Gy.⁵ Eiser has recently reviewed the whole problem of cognitive deficits in children treated for leukaemia.⁶ Clearly they do occur in

many children and for some these are an educational and social handicap. Irrespective of the underlying cause of the problem, remedial help is warranted.

J Rodgers was supported by the Tyneside Leukaemia Research Association.

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Congenital neuroblastoma presenting with paraplegia

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Abstract

A girl presented with paraplegia at birth. A magnetic resonance scan showed an abdominal neuroblastoma with intraspinal extension. Treatment by chemotherapy did not produce any improvement in the neurological signs. Review of previously reported cases suggests the outlook for neurological recovery is poor regardless of treatment.

Case report

A newborn girl, delivered at 38 weeks' gestation by mid cavity forceps, was noted to have bilateral drop foot, a patulous anus with bulging of the perineum, and bilateral subluxing hips. In the hours after birth she dribbled urine

continuously. Plain spinal x ray films showed expansion of the spinal canal between T12 and L2. A magnetic resonance scan showed an extradural tumour extending from T12 to L3, continuous through the intervertebral foramina with a paraspinal mass on the left side (figure). Her homovanillic acid concentration was 38.8 $\mu\text{mol}/\text{mmol}$ creatinine (normal= <20) and hydroxymethoxymandellic acid 30.4 $\mu\text{mol}/\text{mmol}$ creatinine (normal= <9) supporting a diagnosis of neuroblastoma. A biopsy specimen was taken from the abdominal portion of the tumour at laparotomy. Histology showed this to be a poorly differentiated neuroblastoma. At surgery the liver appeared normal and there were no identifiable lymph nodes. The baby was treated with chemotherapy (vincristine 1.5 mg/m^2 , carboplatin 400 mg/m^2 , etoposide 150 mg/m^2 , and cyclophosphamide 600 mg/m^2).

This was well tolerated but there was no improvement in the neurological signs. Her unstable hips were managed in a Von-Rosen splint and her drop foot by ankle-foot orthoses.

Discussion

Congenital neuroblastoma presenting with paraplegia is rare. We have found another 15 cases reported in the literature (table).¹⁻³ In all but one case the tumour appeared to be localised at diagnosis, the exception having hepatic metastases. The treatment given was variable. The majority underwent decompressive laminectomy with, in most cases, postoperative radiotherapy or chemotherapy. Two were treated by chemotherapy alone and none by radiotherapy alone, and one by vitamin B-12 alone. Survival appears good with only two deaths; however, the neurological outcome was very poor.

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Accepted 10 June 1991

(*Arch Dis Child* 1991;66:1246-7)

Magnetic resonance scan showing paraspinal tumour (open arrow) with intraspinal extension (black arrow).