

Growth and hormonal status of children treated for acute lymphoblastic leukaemia

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SUMMARY Growth and hypothalamic-pituitary function have been studied in children in long-term remission from acute lymphoblastic leukaemia (ALL). All 14 children are growing and developing normally; in the 8 children in whom the hypothalamic-pituitary axis was investigated endocrine function is normal. Continuing long-term review of these children is essential, but hypothalamic-pituitary investigation is required only when there is a decrease in growth velocity or delay in the onset of puberty.

Many children treated for acute lymphoblastic leukaemia (ALL) achieve a prolonged remission and probable cure (Mauer and Simone, 1976). This has been accomplished by using combined chemotherapy and central nervous system (CNS) irradiation (Hustu *et al.*, 1973; Medical Research Council Leukaemia Committee, 1973). While the immediate complications of therapy are recognised the possible long-term side effects are uncertain.

Hypopituitarism may follow high-dose irradiation of extra- or intracranial tumours (Tan and Kunaratnam, 1966; Shalet *et al.*, 1975; Richards *et al.*, 1976). Smaller doses of cranial irradiation are used in ALL and it had been hoped that in these children there would be no significant effect on their hypothalamic-pituitary axis. However, recent reports suggest that these children may be at substantial risk of growth hormone (GH) deficiency (Schiliro *et al.*, 1976; Shalet *et al.*, 1976), that their GH responses are related to the dose and fractionation of the irradiation, and that there may be a progressive fall in GH response with increasing time after radiotherapy (Shalet *et al.*, 1976).

This knowledge must influence treatment and long-term management; we have therefore studied the growth and hypothalamic-pituitary function of children in long-term remission from ALL.

Patients and methods

The age range of the 14 children studied was 6.9 to 15.2 years. All were prepubertal at the time of diagnosis. They had been in complete continuous

remission for at least 3.2 years and had received no treatment for at least 1.1 years.

All the children were seen between 1970 and 1974. With the exception of Case 1 they had been treated with the MRC UKALL I or UKALL II protocols. All had received craniospinal irradiation. A Phillips 250 keV machine had been used for the irradiation which was started shortly after induction of haematological remission. The children had received 2000-2500 rads to the cranium in 10-15 fractions for 11 to 18 days. In addition 800 rads had been given to the spinal axis. These details are given in Table 1.

Anthropometric data were available for all the children. Staging of puberty (Tanner, 1962) and skeletal age (Tanner *et al.*, 1962) was according to the described methods. 8 children agreed to undergo a combined hypothalamic-anterior pituitary function test after an overnight fast. Simultaneous intravenous injections were administered of insulin (0.1 U/kg), thyrotrophin releasing hormone (TRH 200 µg), and luteinising-hormone releasing-hormone (LHRH 100 µg) after basal blood samples had been withdrawn through an indwelling 'butterfly' needle. Estimations of blood glucose, plasma GH, cortisol, adrenocorticotrophic hormone (ACTH), serum thyroid-stimulating hormone (TSH), thyroxine (T4), triiodothyronine (T3), follicle-stimulating hormone (FSH), luteinising hormone (LH), and gonadal hormone responses were measured at appropriate intervals. Two hours after the insulin injection oral L-dopa was given as a second stimulus to GH production. The hormones were measured by radioimmunoassay as previously described and the results compared with our values for normal children (Savage *et al.*, 1978).

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Table 1 Clinical details of treatment in children in long-term remission from ALL

Case no.	Sex	At diagnosis		Treatment protocol	Cranial irradiation (fractions)	Time since irradiation (years)	At study		
		Age (years)	Puberty				Age (years)	Bone age	Puberty
1*	M	4.1	P1 G1	Assorted	2400 (12)	5.6	9.8	12.5	P1 G1
2*	M	5.4	"	UKALL I	2000 (10)	5.0	10.5	11.8	P1 G2
3*	M	7.0	"	II	2100 (11)	4.1	11.2	11.2	P1 G1
4*	M	7.1	"	I	2000 (10)	5.4	12.6	14.0	P3 G2
5*	F	2.9	"	I	2500 (15)	5.7	8.7	9.0	P1 G1
6*	F	5.6	"	II	2000 (10)	4.1	9.8	11.8	P1 G2
7*	F	8.7	"	II	2000 (10)	4.2	13.0	13.5	P4 G5
8*	F	9.7	"	I	2000 (15)	5.4	15.2	16.0	P4 G5
9	M	2.7	"	I	2000 (14)	5.6	8.4	—	P1 G1
10	M	4.3	"	I	2000 (10)	4.8	9.2	—	P1 G1
11	F	2.5	"	I	2100 (10)	5.3	7.9	—	P1 G1
12	F	3.7	"	I	2000 (14)	3.1	6.9	—	P1 G1
13	F	5.3	"	II	2000 (12)	3.9	9.3	—	P1 G1
14	F	7.6	"	I	2000 (10)	4.9	12.6	—	P1 G3
Mean		5.5			2080 (12)	4.8	10.4		
Range		2.5-9.7				3.1-5.7	6.9-15.2		

*Endocrine study.

Results

Anthropometric data. None of the children was of short stature, and growth was in accordance with age and stage of puberty (Figs 1 and 2). The mean height velocity of the prepubertal children increased

from 5.9 cm/year (range 4.6-8.6 cm/year) in the year preceding the end of treatment to 8 cm/year (range 5-11.2 cm/year) during the year after stopping treatment. No child had delayed pubertal development.

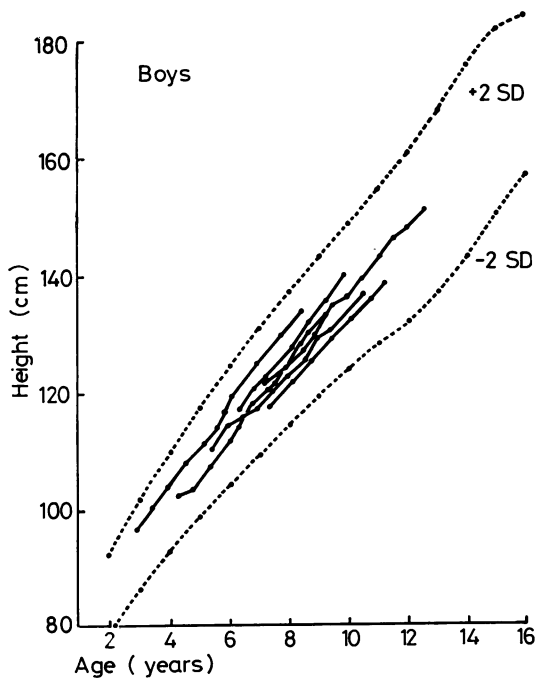


Fig. 1 Growth curves of 6 boys treated for ALL.

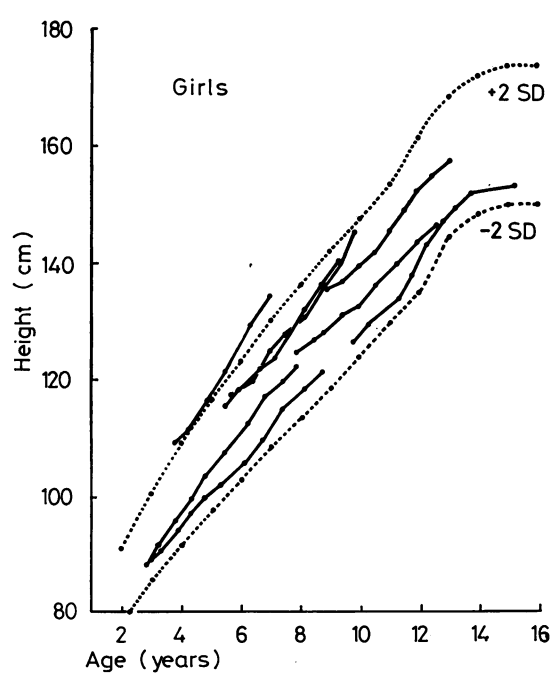


Fig. 2 Growth curves of 8 girls treated for ALL.

Endocrine data.

Growth hormone. Satisfactory insulin induced hypoglycaemia (blood glucose <50% fasting level) was obtained in all 8 children. In our laboratory a normal GH response is a peak level of at least 8 mU/l (Savage *et al.*, 1978). 6 of the 8 children had normal GH responses to hypoglycaemia while all 8 children had normal responses to L-dopa (Table 2).

TSH and thyroid hormones (T4 and T3). Basal TSH levels, with one exception (4.5 mU/l), were all below 3 mU/ml. The peak responses of TSH to TRH were normal (mean 14 mU/l), range 6.2–16 mU/l. Basal T4 and T3 levels and the increment 2 hours after the TRH injection were normal (T4 mean increment 16%, T3 mean 38%) (Savage *et al.*, 1978).

Cortisol and ACTH. Basal cortisol levels were normal or raised, with a range of 250–905 nmol/l (8.9–32.3 µg/100 ml). Cortisol responses to hypoglycaemia were satisfactory in children with normal basal levels, but no response was seen when the basal levels were raised above 600 nmol/l (21.4 µg/100 ml). The range of cortisol levels at 60 minutes after insulin was 425–725 nmol/l (15.1–25.8 µg/100 ml). ACTH measured at 30 minutes after insulin may have missed the peak response (range 17–212 ng/l) but as cortisol values were all normal serial ACTH measurements were not done.

LH, FSH, and gonadal hormones. The LH responses to LHRH were consistent with the children's pubertal status. The LH levels rose from low basal levels (maximum 3.3 U/l) to a mean 30-minute peak of 17.2 U/l (range 7.6–24.3 U/l). The maximum peak response in the prepubertal children was 6.9 U/l. The FSH responses were all within the range seen in normal children.

Before puberty there was, as expected, no rise in serum testosterone or oestradiol 4 hours after LHRH (Savage *et al.*, 1978). Basal levels of gonadal hormones

were related to the stage of puberty and, in the 2 pubertal boys, serum testosterone rose during the LHRH test from 0.68 to 2.16 nmol/l (Tanner Stage P₁G₂) and from 3.3 to 8.8 nmol/l (Tanner Stage P₃G₂). Similarly the 3 pubertal girls showed adequate oestradiol increments related to their stages of puberty.

Discussion

This report evaluates the growth and endocrine function of a group of children in long-term remission after treatment for ALL. The need for such studies has recently been stressed (*British Medical Journal*, 1977). 6 of the 14 children declined investigative endocrine evaluation but this was not surprising as they had all received prolonged and intensive inpatient and outpatient treatment with frequent IV manipulations. None of the 8 children who were fully investigated had evidence of endocrine dysfunction, and as the remaining 6 children were growing normally no attempt was made to persuade them to undergo endocrine testing.

The normal anthropometric data in this study are in general agreement with those found at other centres treating childhood leukaemia, but the GH results are at variance with recently reported studies from Manchester (Shalet *et al.*, 1976, 1977). Although the chemotherapy used in Bristol and Manchester was similar the radiotherapy schedules were different. The Bristol children received approximately 2000 rads in 12 fractions for 15 days using a 250 keV x-ray machine. There was an even dose distribution of cranial irradiation throughout the brain. This dose of 2000 rads has a radiobiological equivalent value similar to 2400 rads using Cobalt (⁶⁰Co) or 4 Mev linear accelerator and the same fractionation regimen. In Manchester a Cobalt (⁶⁰Co) or 4 Mev linear accelerator was used; the children with lower GH responses received 2500 rads or more in 10 fractions for 2½ weeks, whereas those children who achieved higher GH responses had received 2400 rads in 20 fractions for 4 weeks (Shalet *et al.*, 1977).

Ellis (1969) suggested a formula which relates the total radiotherapy dose, number of fractions, and overall treatment time to a quantity termed the nominal standard dose (NSD). This quantity represents the biological effect of a given treatment regimen and allows the effect of different schedules to be compared between centres. Using the Ellis formula the NSD, expressed as rad equivalent therapy (ret) units, given to the Bristol children was 1000 rets. The Manchester children with lower GH responses were given 1070 rets and those with the higher GH responses received 900.

Table 2 *Peak GH response after insulin and L-dopa*

Case no.	GH peak response (mU/l)		Maximum GH peak (mU/l)
	Insulin	L-dopa	
1	7.3	9.4	9.4
2	8.7	16.7	16.7
3	21.0	14.1	21.0
4	11.6	13.4	13.4
5	11.1	13.1	13.1
6	6.1	14.4	14.4
7	14.3	8.3	14.3
8	27.6	36.6	36.6
Mean	13.5	16.2	17.4

The difference of 170 rets in the NSD values of the irradiation given to the two groups of Manchester children could account for the differences found in GH response; the higher dose would be expected to be more damaging to normal tissue. The finding that at a ret value of 1000 given to the Bristol children no lowering of GH response occurred, suggests that the 'safe' upper limit of cranial irradiation in ALL lies somewhere between 1000 and 1070 rets.

Three of the 4 Manchester children reported as having biochemical evidence of GH deficiency were growing normally (Shalet *et al.*, 1976). It is difficult to accept the concept of normal growth velocity with diminished GH reserve, and it remains to be seen whether these children's growth becomes abnormal.

There is considerable variation in the GH results from different laboratories and each must define its own criterion of normality. The Manchester group's definition of an impaired GH response (GH < 20 mU/l after adequate hypoglycaemia) and the insulin dosage are different from ours, but results from a recent Scottish survey show no significant difference in growth velocity between a group of children with GH responses (to insulin hypoglycaemia) of 10–20 mU/l and those with levels greater than 20 mU/l (G. Vimpani, personal communication).

In the present study children with peak GH levels of 8–15 mU/l, which we regard as normal, were growing at a minimum velocity of 5.2 cm/year at the time of study. Furthermore the mean GH peak responses are similar to that of our normal children (Savage *et al.*, 1978).

Diminished GH reserve after cranial irradiation with 2000 rads is reported to be of variable timing with suggestions of an immediate although transient treatment-induced suppression (Dacou-Voutetakis *et al.*, 1975), or the later appearance of GH deficiency. In our study the mean interval between irradiation and the endocrine testing was 4.8 years; there was no relationship between the interval from irradiation and the child's GH response.

There is firm evidence for GH deficiency in children who have received cranial irradiation for intracranial tumours (Shalet *et al.*, 1975; Richards *et al.*, 1976). These patients have often had the associated problems of raised intracranial pressure, neurosurgical exploration, and a much higher dose of irradiation. Their data are therefore not strictly comparable. The possibility remains however that children who have received a lower dose of cranial irradiation may develop diminished hypothalamic-pituitary reserve later.

In an earlier study (Siris *et al.*, 1976) which examined pubertal development in childhood leukaemia, 7 of 35 children were found to have

abnormal gonadotrophin or gonadal steroid levels. But 5 of the 7 were in relapse or had myeloid leukaemia and the remaining 2 later reverted to a normal endocrine and clinical state. In Shalet's group 2 of 7 prepubertal girls were reported as having probable ovarian failure; they suggested that cyclophosphamide was responsible (Shalet *et al.*, 1977). In our study gonadotrophin reserve and gonadal steroid levels were in all cases appropriate for the children's stage of pubertal development. Prepubertally it is not always possible to recognise hypogonadotrophic hypogonadism, and clinical follow-up will decide the validity of the responses in these children. The low LH peak (7.6 U/l) in one postmenarchal girl is compatible with her being in the early follicular phase of the menstrual cycle at the time of testing (McNeilly and Hagen, 1974).

The site of radiation damage to the hypothalamic-pituitary axis is unknown. The pituitary is generally considered to be relatively radioresistant, probably because histological pituitary cell necrosis is rarely seen after irradiation (Lawrence *et al.*, 1971). Radiotherapy may however alter pituitary cell function, increase permeability of the blood-brain barrier to potentially encephalotoxic drugs, or damage the vasculogial tissues of the hypothalamic-pituitary axis affecting the synthesis and release of hypothalamic releasing hormones.

During craniospinal irradiation the thyroid is estimated to receive 500–600 rads. Thyroid cancer has been documented in 7% of patients up to 25 years after receiving radiotherapy for benign childhood conditions of the throat, neck, and chest in doses as small as 300 rads (Refettoff *et al.*, 1975). In contrast, after this amount of radiation primary hypothyroidism is far less common. It is essential therefore to examine the thyroid gland for many years during follow-up after craniospinal irradiation.

Radiotherapists have attempted to find the smallest effective dose of irradiation required to eradicate CNS leukaemia (Hustu *et al.*, 1973). If evidence becomes available that the marginally higher doses of irradiation used in some centres causes GH deficiency, without therapeutic benefit, then the lower effective dose as used in the present series would be advisable. However a clear distinction must be made between what might be a statistically lower response to GH stimulation tests and a real effect on growth and development.

As modern therapeutic regimens allow the real possibility of a cure in many children with ALL and other forms of cancer, the long-term morbidity of various schedules is of great importance. The ongoing care of these children must involve not only a regular review of the treated neoplastic condition but a continuing careful surveillance of growth and

development. We suggest, however, that endocrine investigation is necessary only if growth and development give cause for concern.

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