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Growth hormone and tumour recurrence

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Abstract

***Objective*—To determine whether using growth hormone to treat radiation induced growth hormone deficiency causes tumour recurrence.**

***Design*—Comparison of tumour recurrence rates in children treated with growth hormone for radiation induced deficiency and an untreated population. Computed tomograms from children with brain tumours were reviewed when starting growth hormone and subsequently.**

***Setting*—North West region.**

***Patients*—207 children treated for brain tumour, 47 of whom received growth hormone and 161 children with acute lymphoblastic leukaemia 15 of whom received growth hormone.**

***Main outcome measures*—Tumour recurrence and changes in appearances on computed tomography.**

***Results*—Among children with brain tumour, five (11%) who received growth hormone had recurrences compared with 42 (26%) who did not receive growth hormone. Also adjusting for other variables that might affect tumour recurrence the estimated relative risk of recurrence was 0·82 (95% confidence interval 0·28 to 2·37). The only child with acute lymphoblastic leukaemia who relapsed while taking growth hormone had relapsed previously before starting treatment. Two of the five children with brain tumours who relapsed had abnormal appearances on computed tomography when growth hormone was started. 14 other children who remained relapse free and had follow up computed tomography showed no deterioration in radiological appearance during treatment.**

***Conclusions*—In this population growth hormone did not increase the risk of tumour recurrence but continued surveillance is essential. Abnormal results on computed tomography are not a contraindication to treatment with growth hormone.**

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Introduction

Acute lymphoblastic leukaemia and brain tumours are the two commonest childhood malignancies, the treatment of which has consisted of cranial irradiation with or without adjuvant cytotoxic chemotherapy. Long term management of the endocrine sequelae of treatment, including growth failure, is fundamental to the improved quality of life of these children. The use of growth hormone in children with radiation induced growth hormone deficiency is now widely accepted, but questions still exist about the safety of this mitogenic hormone and whether it might cause a recurrence of a brain tumour or leukaemia.

Studies with small numbers of patients at our centre[1] and others[2,3] suggested that growth hormone is not responsible for recurrence of brain tumours, but none of these studies applied statistical analysis. An analysis of deaths in recipients of pituitary growth hormone showed brain tumour recurrence to be one of the most common causes, but a comparative group who had not received growth hormone was not available for analysis.[4] Therefore, it could not be established whether growth hormone contributed to tumour recurrence.

In children treated with growth hormone after treatment for a brain tumour radiographs of the central nervous system often appear abnormal at the start of treatment. No information is available to determine if

such children are at special risk of a clinically apparent relapse after receiving growth hormone. We therefore compared tumour recurrence rates in a large number of children with radiation induced growth hormone deficiency treated with growth hormone with rates in an untreated population.

Patients and methods

We studied all children aged less than 14·4 years who had brain tumour diagnosed between 1965 and 1989 or acute lymphoblastic leukaemia between 1970 and 1989 in the North West region who were clinically relapse free at least two years after diagnosis. Sixty eight children, 53 with a brain tumour distant from the hypothalamic-pituitary axis (36 boys) and 15 with acute lymphoblastic leukaemia (nine boys) were treated with growth hormone for radiation induced growth hormone deficiency. Six of the 53 children with brain tumours were excluded from the statistical analysis.

In the early part of this study only children with obvious growth failure were referred to the endocrinologist and because of the scarcity of pituitary derived growth hormone only those with the worst growth prognosis received growth hormone. Now that the natural course of radiation induced growth hormone deficiency is better understood all children who are relapse free at two years are assessed for growth hormone deficiency and, with the wide availability of synthetic human growth hormone, all children with growth hormone deficiency are considered for treatment. The tumour prognosis did not knowingly affect patient selection for growth hormone treatment in those with a diagnosis of a brain tumour.

The peak growth hormone concentration on provocative testing with either insulin hypoglycaemia (0·2 U/kg intravenously) or glucagon (15 μg/kg intramuscularly) in all patients treated with growth hormone was less than 15 mU/l. Growth hormone was started at least two years after completion of radiotherapy—that is, after the time when tumour recurrence is most likely to occur. The dose of growth hormone was 12 IU/week before 1989 and 0·5 IU/kg/week after 1989. Twenty three children with brain tumours and six with acute lymphoblastic leukaemia reached final height and discontinued growth hormone.

Each child received cranial irradiation. The median dose to the head was assessed in those who received growth hormone. In children treated for a brain tumour the median dose was 3000 cGy (range 1500-4750) in 20 (8-28) fractions over 27 (9-36) days. In addition, 36 children received a boost to the tumour site (median dose 1500 cGy (range 1000-2000) in 10 (4-11) fractions over 13 (3-22) days). In children treated for acute lymphoblastic leukaemia the median cranial dose was 2400 (1800-4200) cGy in 16 (11-50) fractions over 15 (11-35) days.

Each child with acute lymphoblastic leukaemia received conventional chemotherapy and radiotherapy except one who had already had a haematological and central nervous system relapse. This child was additionally treated with intrathecal radioiodine targeted monoclonal antibodies. Most of the children with brain tumours had had surgery and insertion of a ventriculoperitoneal shunt before radiotherapy. The dose and techniques remained standard throughout the study. The children with brain tumours were randomly assigned to receive chemotherapy, which consisted of vincristine alone or in combination with a nitrosourea, with or without procarbazine over 12 to 18 months.

The records of all children registered with the North West children's cancer registry were reviewed. Diagnosis, treatment details (use of radiotherapy and chemotherapy), relapse-free survival, age at diagnosis, and sex were noted.

Relapse was defined as clinical recurrence of the original tumour either at the primary site, or elsewhere. The first child treated with growth hormone after a brain tumour received initial irradiation treatment in 1965, and the first child treated after acute lymphoblastic leukaemia received irradiation in 1970.

Each child with a brain tumour was regularly reviewed by both the radiotherapist and the neurosurgeon. Computed tomograms taken at the time of starting growth hormone were reviewed and compared with scans taken during follow up.

STATISTICAL METHODS

The primary end point was chosen to be relapse rather than survival; relapse is a marker for survival and the management policy was to consider only children with growth hormone deficiency who were clinically relapse free as eligible for growth hormone treatment. Hence the decision not to start growth hormone in a relapsed child is highly associated with prognosis and results in the self selection of children with a better chance of survival for growth hormone treatment.

Results for children with brain tumours were analysed by Cox's regression model[5] with a time dependent indicator variable,[5,6] taking the values one or zero at time t (measured from irradiation) for each child at risk according to whether the child had or had not received growth hormone by that time. This variable was recalculated for each child still at risk at each relapse time, so a child was considered to be in the no growth hormone group up until the time growth hormone was actually given when he or she switched to the growth hormone group. Allowance was made for other covariates thought to influence relapse free survival—namely, diagnosis, sex, age at diagnosis, and whether or not chemotherapy was included in the primary treatment. As the cases spanned several years and there seemed to be some improvement in prognosis over time, the analysis was stratified by quinquennia of initial treatment—that is, 1965-9, 1970-4 . . ., 1985-9, which permitted different baseline risks of relapse between strata. The Cox models were fitted to the data by using program 2L of the biomedical programs data package.

We excluded from the analysis all children who had relapsed within two years after diagnosis, all those who had not received radiotherapy during primary treatment (and who would therefore not be at risk of radiation induced growth hormone deficiency), six children who received growth hormone therapy within two years after diagnosis, and two other children in whom treatment details were incomplete. Thus 207 children (123 boys) with brain tumours aged between 0·5 and 14·4 years (median 6·7 years) were included in the analysis, 47 of whom (29 boys) received growth hormone. The median length of time from diagnosis to starting growth hormone was 4·5 (range 2·02-10·8) years, and the median duration of growth hormone treatment was 3·2 years.

The Cox model could not be used for the children with a primary diagnosis of acute lymphoblastic leukaemia because only small numbers were treated with growth hormone and there were no first relapses in the treated group. In addition, although selection of patients to receive growth hormone was not knowingly based on prognosis in the brain tumour group, there may have been selection in those children with acute lymphoblastic leukaemia who subsequently received growth hormone. As only one child with a primary diagnosis of acute lymphoblastic leukaemia was treated with growth hormone before at least five years after diagnosis we have reported the relapse numbers of those who were not treated with growth hormone after five years relapse free survival.

Results

BRAIN TUMOURS

Table I shows the characteristics of the children with brain tumours who did and did not receive growth hormone. Five of the 47 children (11%) treated with growth hormone had a clinical relapse associated with recurrence of brain tumour. In two this occurred 1·8 and 4·4 years after completion of growth hormone treatment. In the remainder relapse occurred while receiving growth hormone at 0·5, 0·7, and 3·3 years after starting treatment. One child with an astrocytoma survived the recurrence. Forty two of the 160 children (26%) who did not receive growth hormone relapsed. None of the six children who received growth hormone but were subsequently removed from the analysis relapsed.

TABLE I—*Characteristics of children with brain tumours*

	No (%) not treated with growth hormone (n=160)	No (%) treated with growth hormone (n=47)
Diagnosis:		
Medulloblastoma	43 (27)	26 (55)
Ependymoma	20 (13)	6 (13)
Juvenile astrocytoma	74 (46)	7 (15)
Adult astrocytoma	16 (10)	4 (9)
Other glioma	7 (4)	4 (9)
Year of diagnosis:		
1965-9	41 (26)	4 (9)
1970-4	41 (26)	7 (15)
1975-9	22 (14)	10 (21)
1980-4	29 (18)	18 (38)
1985-9	27 (17)	8 (17)
Sex:		
Male	94 (59)	29 (62)
Female	66 (41)	18 (38)
Age (years):		
<5	50 (31)	22 (47)
5-10	61 (38)	22 (47)
>10	49 (31)	3 (6)
Median age (years)	7·2	5·1
Chemotherapy:		
No	133 (83)	24 (51)
Yes	27 (17)	23 (49)

Table II shows the age at irradiation, time and length of growth hormone treatment, and years of survival since completion of growth hormone treatment in all treated children with and without a tumour recurrence.

Medulloblastoma—In all, 124 children had medulloblastoma diagnosed between 1965 and 1989 in the North West region, 69 of whom were clinically relapse free after two years. Of the 26 who received growth hormone, two (8%) relapsed. One further child died as a result of an accident. Fifteen of the 43 children (35%) who did not receive growth hormone relapsed, four of whom survived. One other child died of a treatment related cause.

Ependymoma—Seventy cases of this poor prognosis tumour were diagnosed between 1965 and 1989. Twenty six of the children were relapse free two years after diagnosis. Two of the six children (33%) who received growth hormone relapsed compared with seven of 20 (35%) who did not receive growth hormone.

Juvenile astrocytoma—142 cases were diagnosed of this relatively good prognosis brain tumour which is not always treated with radiotherapy. Eighty one of the children treated with radiotherapy were relapse free two years after diagnosis. Fourteen of the 74 children (19%) who did not receive growth hormone subsequently relapsed. Two children died of other causes. One of the seven children (14%) who received growth hormone relapsed. She survived the relapse but had a further relapse, although she remained alive despite the presence of disease.

Adult astrocytoma—Twenty of the 86 children were relapse free two years after diagnosis. Four received growth hormone and remained disease free. Four of the 16 children (25%) who did not receive growth hormone relapsed.

TABLE II—*Clinical details of children treated with growth hormone (individual data on children who relapsed and mean data on those who did not)*

Patients	Tumour	Age at radiotherapy	Time from radiotherapy to starting growth hormone (years)	Length of growth hormone treatment (years)	Time to relapse from starting growth hormone (years)	Years since growth hormone stopped
With relapse:						
1	Medulloblastoma	13·1	2·9	3·0	3·4	1·8
2	Medulloblastoma	8·3	3·4	0·7	0·7	*
3	Ependymoma	10·9	2·4	0·4	0·4	*
4	Ependymoma	11·3	2·5	1·0	5·3	4·4
5	Astrocytoma	2·1	9·1	3·3	3·3	12·4*
6	Acute lymphoblastic leukaemia	3·0	8·4	1·7	1·7	2·4*†
Without relapse:						
Growth hormone completed (n=27)		5·4	5·9	4·1		5·1
Growth hormone ongoing (n=29)		4·0	5·0	2·8		

*Relapse while taking growth hormone.
†Previous relapse before starting growth hormone.

TABLE III—*Cox regression analysis on results in children with brain tumour: parameter estimates from full model* stratified by quinquennia of diagnosis*

Variable	Parameter estimate	Standard error	Relative risk	p Value†
Diagnosis (reference=medulloblastoma):				0·24
Z_1 (=1 if ependymoma, 0 otherwise)	0·49	0·43	1·63	
Z_2 (=1 if juvenile astrocytoma, 0 otherwise)	−0·52	0·38	0·60	
Z_3 (=1 if adult astrocytoma, 0 otherwise)	0·17	0·57	1·19	
Z_4 (=1 if other glioma, 0 otherwise)	−0·39	0·78	0·68	
Sex (reference=male):				<0·01
Z_5 (=1 if female, 0 otherwise)	−0·87	0·35	0·42	
Age (reference=≤5 years):				0·18
Z_6 (=1 if >5, and ≤10 years)	0·21	0·37	1·23	
Z_7 (=1 if >10 years)	0·76	0·42	2·15	
Chemotherapy (reference=none):				0·11
Z_8 (=1 if chemotherapy, 0 otherwise)	0·7	0·44	2·02	
Growth hormone‡:				0·71
$Z_9(t)$ (=1 if given by time t, 0 otherwise)	−0·2	0·54	0·82	

*None of the two factor interactions contributed significantly to the model.
†p Value from a likelihood ratio test of omitting each factor from the full model.
‡Note the growth hormone status is recalculated for each patient still at risk at each relapse time.

Other glioma—Twenty seven children had other brain tumours diagnosed that were not classified into one of the previous four categories. Eleven died and five others had relapsed within two years. Of the 11 who remained clinically relapse free at two years, four received growth hormone and none relapsed. Two of seven (29%) who did not receive growth hormone relapsed, one of whom survived. One other child died from a treatment related cause.

The impact on relapse of diagnosis, sex, age, use of chemotherapy in the initial treatment, and growth hormone treatment is shown in table III. The children who received chemotherapy (which was randomly allocated as part of a multicentre trial), had a worse prognosis two years after diagnosis than those who did not receive chemotherapy. Proportionally more children who received growth hormone therapy had received chemotherapy in their initial management than those who did not receive growth hormone. The

TABLE IV—*Estimated relative risks and 95% confidence intervals for impact of growth hormone on tumour recurrence unadjusted; adjusted for age, sex, diagnosis, and use of chemotherapy; and adjusted but excluding the effect of chemotherapy*

	Estimated relative risk	95% Confidence interval
Unadjusted	1·35	0·49 to 3·73
Adjusted	0·82	0·28 to 2·37
Adjusted minus chemotherapy	1·01	0·36 to 2·83

reason for this is not clear, but in these cases there is an apparent protective effect of growth hormone against the risk of relapse.

Table IV shows the estimated relative risk of growth hormone influencing tumour recurrence unadjusted, adjusted for the various parameters above, and adjusted but excluding the effect of chemotherapy. In each case the analysis has been stratified by quinquennia of diagnosis to allow for changing practices in tumour management that may have affected prognosis. In our population the use of growth hormone has not increased the risk of tumour recurrence (adjusted relative risk, excluding chemotherapy 1·01). The size of the confidence intervals, however, suggests that larger numbers will need to be studied for complete reassurance on this issue.

ACUTE LYMPHOBLASTIC LEUKAEMIA

Acute lymphoblastic leukaemia was diagnosed in 484 children between 1970 and 1989 in the North West region. In all, 161 children were relapse free at five years, and 14 had received growth hormone. One other child who received growth hormone relapsed (table II). He had had two previous relapses before starting growth hormone but was thought to have a reasonable prognosis at the time treatment was started. No child who had been relapse free when growth hormone was started subsequently relapsed. Eleven of 147 (7%) children who did not receive growth hormone relapsed and a further three died of other related causes.

No child who received growth hormone developed a second primary tumour and no child treated for brain tumour and subsequently with growth hormone developed leukaemia.

COMPUTED TOMOGRAPHY

Forty four children with brain tumours had computed tomography around the time of starting growth hormone (mean 1·4 (SD 1·3) years before growth hormone started). Apart from changes resulting from surgery and radiotherapy in 19 children computed tomography showed other abnormalities. In 10 children the scans showed residual tumour and in nine non-enhancing low attenuation or cystic lesions in the area of the original tumour.

The five children with brain tumours who had relapsed had had computed tomography when growth hormone was started. One had evidence of residual tumour and one had a low density non-enhancing lesion. In four children subsequent relapse was confirmed by finding an enhancing tumour on computed tomography. In the fifth child clinical relapse was confirmed by cerebrospinal fluid cytology before a lesion became apparent on computed tomography.

Of the 39 children who had scans around the time of starting growth hormone but who had not clinically relapsed, 14 had subsequent scans up to 14·9 years after starting growth hormone (mean 3·7 (SD 4·4) years). Four children with follow up scans had residual tumour at the time of starting growth hormone. In two the follow up scan showed no residual tumour and in the other two children there was no notable change in scan appearance. In three other children computed tomography showed an area of low density at the time of starting growth hormone. In one of these children a subsequent scan appeared normal and in the other two there was no change on follow up. None had a deterioration in appearance of the residual lesion. The other scans, which showed no residual tumour when growth hormone was started remained unchanged on follow up. One child whose scan showed residual tumour when growth hormone was started subsequently died as a result of an accident 1·3 years later. At postmortem examination there was no evidence of residual tumour.

Discussion

Most children receiving cranial irradiation with a dose in excess of 24 Gy for treatment of brain tumours or leukaemia will become growth hormone deficient after five years; the speed of onset of growth hormone deficiency is dose dependent.[7] It is now recognised that the ultimate height in these children is further compromised by early puberty and, in those receiving craniospinal irradiation, poor spinal growth. We therefore now aim to start growth hormone treatment in children who are growth hormone deficient at a time at which relapse is less likely but before there has been an appreciable decrease in stature. In our unit the dose of growth hormone is now based on weight. Therefore we would expect that the length of time on growth hormone and the dose per kg (except when the weight is less than 24 kg) for an individual child has increased in recent years.

Growth hormone is mitogenic, and there is evidence in animals of a cause and effect relation between supraphysiological doses of growth hormone and development of acute leukaemia.[8,9] In addition, in vitro data have shown that growth hormone and insulin-like growth factor 1 promote leukaemic blast cell replication from human marrow.[10] In animals the incidence of solid tumours is increased after giving growth hormone. In female rats lymphosarcomas of the lung, adrenocortical and adrenomedullary carcinomas, ovarian tumours, and breast tumours have been described after giving growth hormone.[11] In patients with acromegaly, in which a high growth hormone concentration is pathologically sustained, there is a significantly increased incidence of cancer in general.[12] Development of acute lymphoblastic leukaemia has been reported de novo in children receiving growth hormone either for idiopathic growth hormone deficiency or after treatment of a brain tumour.[13,14] But although the incidence of leukaemia may be slightly increased after growth hormone treatment in growth hormone deficient patients, it is not clear that this can be attributed to growth hormone.[15] In our study the only child with acute lymphoblastic leukaemia who relapsed while taking growth hormone was at high risk because of the two previous relapses of leukaemia; furthermore, no child with a primary diagnosis of brain tumour developed acute lymphoblastic leukaemia after receiving growth hormone.

INTERPRETATION OF STUDY

The North West tumour registry has allowed us to obtain accurate data on children with the same tumour diagnosis in whom growth hormone was not used. As well as documenting non-fatal tumour recurrence or persistent disease, the registry differentiates death from causes other than tumour recurrence. For each child there are accurate records of treatment. It is therefore encouraging that in each tumour category, in which the prognosis differs, there was no association between growth hormone therapy and tumour recurrence.

Several children had abnormal appearances on computed tomography when growth hormone was started. The reasons for the abnormalities include postoperative features, radiation changes, or residual or recurrent tumour. Even those reported as showing residual tumour were not more likely to show evidence of progression of the lesion on follow up scanning. We found no evidence that abnormal results on computed tomography should be a contraindication to starting growth hormone treatment.

The results of an earlier study from this centre (the patients representing a subset of the current population) suggested growth hormone was not responsible for tumour recurrence.[1] In that study fewer children with radiation induced growth hormone

deficiency were treated with growth hormone, at a lower individual dosage, and for a shorter time. With the more widespread use of growth hormone, and particularly with its current use in immunosuppressed patients, review of its safety is essential. Children treated with cranial irradiation account for the largest group of children with growth hormone deficiency due to an organic lesion, and growth hormone has proved benefits in this group. It is encouraging that there is no increased risk of tumour recurrence in our children in whom growth hormone therapy has been used. Caution must still exist, however, and continuing surveillance is crucial.

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Effect of serotesting with counselling on condom use and seroconversion among HIV discordant couples in Africa

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Abstract

***Objective*—To determine whether HIV testing and counselling increased condom use and decreased heterosexual transmission of HIV in discordant couples.**

***Design*—Prospective study.**

***Setting*—Kigali, the capital of Rwanda.**

***Subjects*—Cohabiting couples with discordant HIV serology results.**

***Main outcome measures*—Condom use in the couple and HIV seroconversion in the negative partners.**

***Results*—60 HIV discordant couples were identified, of whom 53 were followed for an average of 2·2 years. The proportion of discordant couples using condoms increased from 4% to 57% after one year of follow up. During follow up two of the 23 HIV negative men and six of the 30 HIV negative women seroconverted (seroconversion rates of 4 and 9 per 100 person years). The rate among women was less than half that estimated for similar women in discordant couples whose partners had not been serotested. Condom use was less common among those who seroconverted (100% *v* 5%, p=0·01 in men; 67% *v* 25%, p=0·14 in women).**

***Conclusions*—Roughly one in seven cohabiting couples in Kigali have discordant HIV serological results. Confidential HIV serotesting with counselling caused a large increase in condom use and was associated with a lower rate of new HIV infections. HIV testing is a promising intervention for preventing the spread of HIV in African cities.**

Introduction

The major route of HIV transmission in Africa is heterosexual intercourse.[1-3] Genital ulcerations, use of hormonal contraceptives, lack of male circumcision, and the clinical status of the index case have been implicated as risk factors in transmission of HIV.[2 4-8] As with gonorrhoea, gender is also thought to have a role, with male to female transmission being more efficient than female to male transmission.[9] However, the importance of these factors in explaining the high prevalence of infection in Africa and their utility in designing effective prevention programmes are unknown.

Cohort studies of HIV discordant couples (one partner HIV positive, the other HIV negative) that monitor the risk factors, sexual behaviour, and HIV status of both partners over time provide data for examining the determinants of heterosexual transmission. Studies of discordant couples in the United States have found a wide variation in reported rates of infection among the heterosexual partners of people infected with HIV[6 10]; the lack of a detectable association between the number of acts of sexual intercourse and the risk of infection[9 11-13] suggests the presence of other factors affecting HIV infectivity and susceptibility.

The aim of this study is to evaluate the effectiveness of a prevention programme linking confidential HIV serotesting with a programme for counselling and providing condoms to urban couples. We report here the factors associated with risk reduction (particularly, the use of latex condoms) and seroconversion among 53 HIV discordant couples followed prospectively for two years in the capital of Rwanda in Africa.

Subjects and methods

SUBJECTS

In 1986 the Projet San Francisco was established in Kigali, Rwanda, by the University of California in San Francisco in collaboration with the National AIDS Program of Rwanda. During 1986 and 1987 a consecutive, population based sample of 3702 women aged 18-35 was screened for HIV at the prenatal and paediatric outpatient clinics of the Centre Hospitalier de Kigali.[14] Stratified random samples of 460 HIV positive and 998 HIV negative women were recruited in 1988[15] for longitudinal studies of the predictors of