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Adult survivors of childhood acute lymphoblastic leukaemia with GH deficiency have normal self-rated quality of life but impaired neuropsychological performance 20 years after cranial irradiation

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Abbreviated title: Childhood acute lymphoblastic leukaemia and intellectual function.

Key words: Acute lymphoblastic leukaemia, neuropsychological performance, quality of life, GH deficiency

Abstract

Objective Cranial radiotherapy (CRT) was until recently, important for achieving long-term survival in acute lymphoblastic leukaemia (ALL). Because survival rates have markedly improved, the long-term complications, such as GH deficiency (GHD) and neuropsychological impairment, has become increasingly important.

Design and Patients The level of self-reported quality of life and neuropsychological functioning was investigated in 44 adults (21 women) with a median age of 25 years who had been treated for childhood onset (CO) ALL with CRT (median 24 Gy). Comparison was made with matched population controls. A subset of patients with GHD were evaluated for neuropsychological functioning after one year of GH treatment.

Results Compared to controls, the patients had significantly lower performance in neuropsychological tests. Early age at treatment had a significant negative impact on neuropsychological performance in adulthood. No relationship was found between dose of CRT, time since treatment of ALL or gender and neuropsychological performance. Compared to controls, the patients did not show a poor quality of life or a lowered availability of social interactions or social networks; however, significantly more patients were living alone or with their parents. After GH-testing, the patients were all considered GHD or insufficient, but no relationship was observed between stimulated peak GH secretion and neuropsychological performance. Treatment with GH for one year in a subgroup of the patients did not improve their neuropsychological performance.

Conclusions This study showed that adults treated with CRT for CO ALL had GHD and significantly impaired neuropsychological performance, although self-reported

quality of life was not affected. The effect of GH treatment in this patient group has to be further elucidated.

Introduction

Acute lymphoblastic leukaemia (ALL) accounts for one quarter of all childhood cancers and is the most common childhood malignancy.¹ To prevent central nervous system relapses, prophylactic cranial radiotherapy (CRT) together with multiagent therapy including intrathecal methotrexate (MTX) was considered important for achieving long-term survival of patients with childhood onset (CO) ALL and survival has improved greatly to approximately 80%.¹ However, CRT at doses of 18 to 24 Gy,^{2,3} with intrathecal MTX⁴ resulted in intellectual impairment.³ More substantial declines in IQ have been associated with young age at CRT⁵⁻⁹ and girls seem to be more vulnerable.^{2,7,10} A decline in intellectual functioning has been shown 4-8.5 years after treatment with 18-24 Gy of CRT,¹¹ but information on longer follow-up is missing.

Another problem for these patients is hypothalamic-pituitary hormone insufficiency which is a well recognized sequel of external CRT for childhood brain cancer.¹² A significant occurrence of GHD has been shown in adults treated in childhood with lower doses of CRT, e.g. in CO ALL.^{13,14} GHD is usually the first and often the only established endocrine sequel of CRT.¹⁵ Patients with GHD due to primary hypothalamic-pituitary disease are known to experience reduced quality of life^{16,17} and neuropsychological dysfunction.¹⁷⁻¹⁹

Previous studies after CO ALL have assessed neuropsychological functioning in childhood or during adolescence but not in adulthood. Neuropsychological dysfunction has also not previously been related to a possible decline in GH secretion in this patient group. Quality of life assessed by telephone interviews in

adults with CO ALL showed a greater negative mood,²⁰ poorer interpersonal functioning and problems in coping with relationships and friendships, compared to controls.²¹ However, there is no information on this patient group with respect to their self-rated quality of life or social functioning.

One aim of the present study was to assess neuropsychological functioning and the accomplished educational level in 44 adults who had survived CO ALL and who were at least 18 years old at the time of study. A further aim was to investigate their self-rated quality of life, social interactions and social networks. Comparison was made with matched controls from the general population. Furthermore, a subset of former ALL patients with GHD were evaluated for neuropsychological functioning after one year of GH treatment.

Subjects and Methods

Patients

Adult patients treated for CO ALL with chemotherapy and CRT during 1971-1992 at the Children's Hospital, Lund, were invited to participate. Patient characteristics, including previous treatments, and the cardiovascular risk factors have been described in a previous report.¹⁴ Briefly, the study included 44 patients (23 male, 21 female) with a median age of 24.8 years (range 19.8-31.3), who had been diagnosed with ALL at a median age of 4 years (1-17 years). The patients had been treated with CRT, at a target dose of 24 Gy (18-30), at a median of 20 years previously (8-27), and had been off chemotherapy for a median of 16.7 years (6.3-23.9).

The children had been treated according to the Swedish Child Leukaemia Group protocols²² until 1981 and thereafter according to common protocols in the five Nordic countries.^{23,24} From prognostic factors, risk was assessed according to varying treatment intensity as standard (SR), intermediate (IR) and high (HR), with 29, 1 and 14 patients allocated to each risk group, respectively. All patients diagnosed with ALL from 1971 to 1981 received CRT; from 1982 to 1992, children in the SR and IR groups received no CRT and were therefore not eligible for the present study. CNS therapy included prophylactic CRT (1.7 Gy/fraction) and intrathecal MTX; chemotherapy was described previously.¹⁴ Five patients had received CRT in combination with spinal radiation (median 23.0 Gy, range 14-25 Gy) and 12 boys received radiation to the testes. Five patients had been treated for relapse, one patient for more than one relapse, and one patient had been treated with high dose chemotherapy with autologous stem cell rescue.

GH treatment in childhood had been given to 4 patients, though not for at least 5 years. One female had primary amenorrhea and 5 were using estrogen contraceptives. Thus, all but one female had isolated GHD or GH insufficiency. Testosterone was appropriately administered to 10 of the 12 males who had received radiation to the testis; one male had not been properly irradiated due to an undescended testis and had normal testosterone levels, while the other was not sufficiently substituted. Thus, all but 11 males, who were given sufficient testosterone substitution, had isolated GHD or GH insufficiency. There was also one male patient receiving thyroxine replacement. No significant differences were recorded in the serum levels of TSH, FT4, FT3, testosterone, estradiol, and cortisol between patients and controls (data presented elsewhere¹⁴).

Control subjects

The intention was to select one control subject for each patient enrolled in the study, and method of selection was the same as that described previously for the investigation of cardiovascular status.¹⁴ Potential control subjects, matched for age, gender and residence (rural/non rural), were randomly selected from a computerized register (Southern Swedish Medical Region) of the population in the local area of the patients. Potential controls were contacted by telephone, were then also matched for smoking habits and, for each patient, the first eligible control that agreed to participate in the study was chosen.

Study design

The Ethic's Committee of Lund University approved the study protocol and all subjects gave written informed consent. For each patient and control, all investigations were performed on a single day, except for the GH stimulation tests.

All patients and controls underwent a GHRH-arginine test.²⁵ After an interval of at least one month an additional insulin tolerance test (ITT) was performed in each patient; however, the ITT results could not be used for five patients: one due to technical problems and four due to failure to achieve acceptably low blood glucose levels in spite of a repetition of the test.²⁶ The ITT was performed after an overnight fast with 0.1-0.2 U/kg iv soluble insulin (Actrapid, Novo Nordisk A/S, Bagsvaerd, Denmark). Severe GHD was defined as a peak GH response $<3 \mu\text{g/L}$ to an ITT^{26, 27} or $<9 \mu\text{g/L}$ during the GHRH-arginine test.²⁸ GH insufficiency was defined as a peak GH of $3\text{-}5 \mu\text{g/L}$ during the ITT²⁹ and $9\text{-}16.5 \mu\text{g/L}$ during the GHRH-arginine test.²⁵ When the GH response to the GHRH-arginine test was >9

µg/L and the ITT in the same patient was <3 µg/L, the ITT result determined the GHD classification, according to Darzy et al.²⁹ On this basis, 40 of the former ALL patients (91%) were considered to have severe GHD and 4 patients were considered to be GH insufficient. The median peak GH during GHRH-arginine was significantly lower in patients compared to controls (6.2 µg/l vs 23.9 µg/l, (P<0.001).¹⁴ This was also true for the serum IGF-I levels (142 µg/L vs 253 µg/L; P=0.004).

Fourteen patients with severe GHD and 14 control subjects agreed to participate in a one-year follow-up, comprising a repeat neuropsychological examination. The former ALL patients were treated during the one-year period with biosynthetic human GH (Humatrope, Eli Lilly and Company, IN, USA) by daily subcutaneous injection. The commencing dose was 0.1 mg and within 4-6 weeks the dose was increased to 0.5 mg and then adjusted according to the serum IGF-I, where the aim was an IGF-I concentration in the middle of the age adjusted reference range. The median final GH dose was 0.4 mg/day (range 0.2-0.6). The dose of GH was reduced in three patients due to side-effects of arthralgia.

Biochemical assays

Serum IGF-I was assayed by immunoradiometric assay (Nichols Institute of Diagnostics, San Juan Capistrano, CA, USA); the normal range was 122-400 µg/L in subjects aged 19-40 years. The intra-assay CV was 16% at the level of 60 µg/L and 11% at the level of 300 µg/L. Serum GH was analysed by an immunofluorometric method (DELFI hGH, Wallac Oy, Turku, Finland); the

detection level was 0.01 µg/L and the intra- and inter-assay CVs were 5% and 3%, respectively, at 1.5 µg/L, and 3% and 5%, respectively, at 7.7 µg/L. The kit standards were calibrateded against the first IS 80/505 International Standard and the assay was specific for GH 22kD.

Quality of life questionnaires, social interaction and social network

Quality of life was assessed by two self-rating questionnaires. The Symptom Checklist-90 (SCL-90) comprised 90 items expressing psychosomatic and emotional distress³⁰ and yielded nine sub-scales. The Global Severity Index (GSI), calculated as the average score of all 90 items, represented the overall level of distress. The quality of life instrument – AGHDA- is a tool for the assessment of quality of life in adults with GHD.³¹ The format is thus disease-oriented and consists of 25 statements to which a “yes” or “no” response is requested. The score range for the AGHDA is 0-25; a score of 25 represents the greatest morbidity.

The Interview Schedule for Social Interaction (ISSI) is a self-reported questionnaire about the quantity and quality of social support.^{32,33} It consisted of 33 items combined into four scales measuring availability and adequacy of attachment, as well as availability and adequacy of social integration.

The 16-item Social Network questionnaire reflected the structural level, i.e. the availability of social support but not the subjective experience of its adequacy.³⁴⁻³⁶

Availability of *instrumental support* reflected the access to practical services and material resources, and availability of *emotional support* reflected the opportunity for care, encouragement of personal value, and feelings of confidence and trust.

Social anchorage reflected to what degree the individual belonged to formal and informal groups in the social network, and the degree of feeling of membership in these groups. *Social participation* indicated how actively the individual took part in activities of formal and informal groups in society.

Neuropsychological tests

All subjects were examined individually with a battery of neuropsychological tests, administered by the same psychologist. All manual scoring was cross-checked by a second psychologist. For every participant the tests were given in the same fixed sequence. The selection of tests was governed by a demonstrated high sensitivity for subtle brain dysfunction,³⁷ while covering a wide array of functional domains. The battery comprised the following tests: *SRB:1 vocabulary*,³⁸ a verbal knowledge or intelligence test containing 30 items of the multiple-choice type; *WAIS-R Information*, a test of contemporary and historical knowledge,³⁹ *WAIS-R Digit Symbol test*,³⁹ a test of perceptual and fine motor speed; *WAIS-R Block Design test*,³⁹ measuring spatial, logical and speed abilities; *Cronholm-Molander verbal memory test*⁴⁰ an associative learning task, comprising immediate and delayed recall sections. For the one-year follow up after GH treatment a parallel version of stimulus words was used. *Austin Maze test with the Milner pathway*,^{41,42} a test of executive functions involving spatial learning, strategy and speed in a modified computerised video screen version. The test was abbreviated to 10 trials, and total errors and performance time refers to the memory trials. In addition, a parallel version of the maze was used: *APT Two-way Reaction Time test* (APT RT-2), a computer-assisted test from the Automated Psychological Test System.⁴³ Stimuli were randomly presented on the left and right side of a computer screen and

corresponding dual response keys were used. Results were expressed in terms of level (the mean of 50 individual RT responses) and variation (the SD of 50 individual RT responses). *APT Inhibition test* (APT RT-Inhibition), a test similar to APT RT-2 with the addition of a randomly appearing auditory alarm presented simultaneously with the visual signal (ratio 0.50), whereupon the subject was required to inhibit the response; results were expressed as for APT RT-2, with the addition of an error ratio (i.e. false hits). *APT k-test*, a test of sustained attention, requiring continuous scanning of a computer screen containing up to 10 letters for the presence/absence of a critical stimulus, the letter k. The subject's task was to respond correctly and as quickly as possible to each stimulus set by pressing the corresponding keys ('k' vs. 'no k'); around 100 stimulus sets were presented during 5 minutes and results expressed (a) according to the Signal detection theory⁴⁴ as d' (accuracy) and β (balance between hits to targets and false hits to non-targets), (b) as RT level depending on stimulus laterality (the mean of the single RT responses for correct hits, left-center-right), (c) as error ratio (proportion of missed and false hits), and (d) as search strategy (the RT ratio for correct yes/no responses with k present/absent, indicating the search strategy on a global vs. sequential scale; a higher value indicating a more global strategy).

To supplement the basic analysis of raw scores from the neuropsychological tests, each subject's mean z-score across all nine tests was calculated to provide a summary measure of performance. After computing a standardized z-distribution for each test based on the test scores obtained in the control group (i.e. in the control group the mean z-score for every test variable was 0 [zero] and the SD was 1.0), the performance of each patient on each test was calculated relative to the

standardized distribution. For any test providing more than one variable (e.g. the Austin Maze test) a single summary z-score was computed as the mean z-scores of all variables of the test (except the k-test where z was based only on the three RT variables), in order to secure an equal weighting of each test in the final summary z-score. Finally, the resulting nine z-score variables, each representing one test, were summarized in a total mean z-score for each patient.

School education and marital - social status

School education was rated at three levels i.e. nine years of elementary school, secondary school or studies at university level. All forms of education after secondary school was classified as studies at university level. Marital and social status was investigated with a questionnaire.

Statistical analysis

Data were analyzed with SPSS, version 11.5. The level of statistical significance was set at $P < 0.05$. The matched pairs of patients and controls were compared with the Wilcoxon's signed rank test, which was also used to study the neuropsychological scores at one year follow-up. For this analysis, each patient's score on each test variable in the first examination was subtracted from the follow-up score, and the Wilcoxon's signed rank test was used to compare the difference between scores for the matched pairs. The independent effects of (i) years since CRT treatment, (ii) age at CRT treatment, (iii) peak GH response during the GHRH-arginine test, and (iv) dose of CRT, on neuropsychological performance among patients (total mean z-score), were evaluated with linear multiple regression based on ranked data. Mann-Whitney's U-test was used for comparisons between

subsets of patients. Differences in educational level and social status were tested by the McNemar's test for correlated proportions.

Results

Quality of life measures, social interaction and social network

No statistically significant group differences were observed across any of the nine SCL-90 subscales, nor for the overall distress measure GSI (Table 1). No significant difference was recorded in AGHDA scores between patients and controls [median 5.0 (range 0-25) and 3.5 (0-18), respectively ($P=0.30$)]. Six out of 44 patients and 4 out of 44 controls, respectively, had an AGHDA score ≥ 11 . The patients did not show any statistically significant difference in social interaction compared to controls. Among the social network parameters only emotional support showed a tendency of being somewhat lower in the former ALL patients than among controls ($P=0.07$). For each of these analyses, there was no influence of gender on the results (data not shown).

Educational, social- and marital status

A significantly lower level of education was recorded among patients, with 23% reaching university level compared to 55% in the control group ($P=0.01$). Within the patient group there was no obvious association between age at treatment and level of school education (data not shown).

Four of the patients and 7 control subjects were married, which was not significantly different ($P=0.45$). However, significantly more patients than controls (28 patients vs 17 controls; $P=0.019$) were living alone or together with parents.

Neuropsychological tests

Compared to controls, the former ALL patients had a generally lower performance in neuropsychological tests, reaching statistical significance in 14 of the 20 test variables (Table 2). The ALL group scored lower than controls in tests of general knowledge and vocabulary ($P=0.001$), and in the test for spatial ability and speed (WAIS-R Block Design) ($P<0.001$). Moreover, in tests of short-term memory functions a slower rate of learning was observed in the Austin Maze test ($P=0.018$) and lower scores were found in Cronholm-Molander immediate and delayed recall ($P=0.009$ and $P=0.006$, respectively). Lower performance was also seen in the perceptual and fine motor speed test (WAIS-R Digit Symbol) and in the psychomotor speed tests of the reaction time type (APT RT level and variation and the RT level of the k-test), (P-values ranging from <0.001 to 0.014). However, on some tests, the 'accuracy' dimension of responses was less clearly reduced among ALL cases compared to controls and did not reach statistical significance (errors in Austin Maze and k-test, RT failed inhibition ratio, and the d' and Beta variables in k-test). Gender showed no general relationship with test performance (data not presented).

The summary measure of performance, the mean z-score across all tests, was lower in the patient group than among controls ($z = -0.95$; $P<0.001$). Multiple regression showed that lower age at CRT treatment was related to poorer neuropsychological outcome ($\beta=0.52$; $P=0.004$). Time since CRT treatment showed only a tendency to be related to neuropsychological outcome, although in the opposite direction to what was expected ($\beta=0.29$; $P=0.08$; i.e. longer time since treatment tended to be related to higher performance). Neither the dose of CRT ($\beta= -0.006$; $P=0.97$), nor

peak GH during the GHRH-arginine test ($\beta = 0.09$; $P = 0.5$), were related to neuropsychological performance. Closer examination of the relationship between age at CRT treatment and neuropsychological performance showed that patients given CRT before the age of six had significantly lower mean z-score across all tests ($z = -1.18$; $n = 27$) than those treated at a higher age ($z = -0.66$; $P = 0.019$; $n = 17$). A wider variation in performance was observed within the early treatment group, with a subset of patients having particularly low mean z-scores (Figure 1). While 10 of the 27 patients treated with CRT before the age of six had a mean z-score in the range -3.4 to -1.5, none of the 17 patients treated at a higher age had a mean z-score below -1.3.

The effect of one year of GH treatment on neuropsychological functioning and on serum IGF-I levels

A tendency for improvement was shown across all tests in both groups for the 14 patient-control pairs. However, only a few test variables showed a statistically significant improvement. Among the 14 patients, improvements were seen in 4 of 20 variables: the Cronholm-Molander test (median scores for baseline and 1 year, respectively: immediate recall: 20.0 vs. 23.5, $P = 0.004$; delayed recall: 18.5 vs. 20.0, $P = 0.013$) and the APT RT-Inhibition (medians for level: 478 ms vs 429 ms, $P = 0.048$, medians for variation: 102 ms vs 78 ms, $P = 0.048$). The 14 controls also showed improvements in 4 of the 20 variables: the WAIS-R Information test (median scores: 20.0 vs 21.5, $P = 0.020$), the WAIS-R Block design test (median scores: 29.0 vs 39.0, $P = 0.049$), and the APT RT-Inhibition (medians for level: 408 ms vs 353 ms, $P = 0.013$, medians for level 91 ms vs 62 ms, $P = 0.026$). However, the differences (improvements) in test scores, between the initial testing and the one

year follow up, did not differ between patients and controls for any of the 20 test variables, with the exception of WAIS-R Information test scores, which improved only in the control group (median improvement: 0 vs. 2.0, $P=0.030$).

Serum IGF-I levels increased significantly after one year of GH treatment (median 139 vs 253 $\mu\text{g/L}$, $P=0.002$). Expressed as SDS IGF-1 the median value was -1,2 (-3,0-+1,0), before treatment and after one year of GH treatment it was +1,0 (-3,0-+1,1),

Discussion

This study showed that patients who survived CO ALL until adulthood had impaired performance in neuropsychological tests at a median 20 years since CRT and 17 years since completion of chemotherapy. The former ALL patients had significantly lower test scores than controls in tests of vocabulary and general knowledge, spatial ability, memory and learning, and perceptual and psychomotor speed, as well as a lower educational level. A significantly negative impact on neuropsychological performance in adulthood was seen for age at CRT, but there was no relationship with dose of CRT, gender or time since treatment of ALL. The patients were all GHD or insufficient, but no correlation was recorded between the remaining GH response and neuropsychological test scores. One year of GH treatment in a subset of the former ALL patients, did not improve scores in neuropsychological tests.

The strength of this study is that it is the longest follow up (median 17 years) of a homogenous group of adult survivors of CO ALL, treated with cranial irradiation and chemotherapy, including intrathecal MXT. Another, strength is the appropriate control group, randomly recruited from the general population and matched for age, gender, smoking habits and residence. Because a similar percentage of potential controls (7%) as ALL patients (5%) declined participation due to health reasons, we consider it unlikely that the recruitment of the control group resulted in any important selection bias. We were not able to include a control group of non-irradiated ALL patients, as no such group was available that were comparable with respect to risk group classification, calendar-year of diagnosis, length of follow up and chemotherapy schedule.

The tests used in this study to evaluate neuropsychological performance are well established and validated.^{17, 37,39} Further, to eliminate possible effects of an examiner-specific variation, the neuropsychological examination was administered by the same psychologist both at baseline and at one year follow-up.

Previous studies of psychosocial sequelae in adults who survived CO ALL, have shown greater negative mood disturbances with more symptoms of depression, confusion, tension and anger as compared to siblings.²⁰ Also poorer self image and greater psychological distress have been shown in patients receiving CRT compared to those treated with intrathecal MTX without CRT.⁴⁵ This is in contrast to the present study where no difference in any of the SCL-90 subscales could be detected. In addition, when using the disease specific quality of life questionnaire for adult GHD AGHDA, did not change these results. A possible explanation may

be that these patients had developed coping strategies and adapted to their situation. This mechanism has been suggested for patients with CO GHD, who reported fewer disturbances in quality of life than those with adult onset GHD.^{46,47} In the present study, 91% of the ALL patients were GHD and the rest were GH insufficient, and the GH impairment had probably existed for some time.⁴⁸ It seems however, that there is a marked mismatch between perceived quality of life in subjects with CO GHD and their behaviour and social and economic achievements.⁴⁹ Thus, it has been suggested that self-rating questionnaires may underestimate the true impairment of quality of life in CO GHD patients.^{47,50}

In irradiated GHD adult survivors of childhood brain tumours, who were selected on the basis of self-rated poor quality of life to receive GH treatment, a marked improvement could be recorded after GH treatment.⁵¹ These adult survivors of childhood cancer were treated with higher doses of CRT and at an older age (13 yrs) than the patients in the present study. However, no information of neuropsychological functioning was recorded in the study by Mukherjee *et al.*,⁵¹ In addition, another more disease specific quality of life questionnaire for GHD used in a selected cohort of patients in the transition phase from end of puberty to adulthood, have shown significant differences at baseline in parameters as self-assessed body shape and sexual behaviour.⁵²

In a previous study⁵³ it was shown that adult survivors of CO ALL reported poorer interpersonal functioning and coping for love/sex relationships and friendships, compared to controls. This is partly in contrast to the present study in which the patients reported no significant difference in the quantity and quality of social support. Again, in the study by Mackie *et al.*,⁵³ the information was based on

interviews and not on self-rating questionnaires, which may have influenced the results. Circumstantial evidence that the patients in the present study may have overestimated their social interaction and support was that significantly more of them still lived alone or with their parents, compared with their age-matched controls. This is in accord with the finding of Dean *et al.*⁵⁴ who recorded that the percentage of patients with CO GHD who were married was 30% less than would be expected for their age. No difference in current treatment of depression was recorded between patients and controls in the present study, which is consistent with a previous study.⁵³

In children treated for ALL, long-term assessment of musculoskeletal and gross motor function, including strength, balance, hand grip and running speed, has shown poorer performance than in age and sex matched controls.⁵⁵ Even if no statistically significant difference was found between the groups who had received CRT and those who had not, the scores for the children who had received CRT indicated greater impairment and disability in most parameters.⁵⁵ Also fine and gross motor evaluations have shown significantly poorer functions than in age and sex matched controls.⁵⁶ In parallel, the former ALL patients in the present study showed a slower performance in the perceptual and fine motor speed test (WAIS-R Digit Symbol) compared with the controls.

Impairment of short term memory and attention has previously been reported in CO ALL treated with both 18 and 24 Gy.⁷ The mechanism was suggested to be a lower strategic planning behaviour affecting memory recall.⁵⁷ This agrees with the results of the present study, showing lower scores in tests of spatial learning and verbal memory. Attentional deficits, in comparison to sibling controls, were also recorded

in a group treated with 18 Gy and intrathecal MTX,⁵⁸ which is in accordance with the impairment of sustained attention recorded in the present study.

The neurocognitive impairments shown in former ALL patients, lead to a greater likelihood of being placed in special education or learning-disability programs than siblings,^{5,9} and a significantly lower number of former ALL patients enter secondary education or college.^{5,9} This is consistent with the present study where a disproportionably low number of former ALL patients reached university level. In previous studies, early age at diagnosis was the risk factor most related to low educational level.^{5-7,9} Our results did not support this, comparing subjects diagnosed up to 6 years of age with those diagnosed later. On the other hand, we observed that the mean neuropsychological test score for the patients correlated strongly with age at treatment. However, longer time since CRT treatment was not shown to have an adverse effect on neuropsychological performance in a regression model including control for age at CRT treatment. This is a novel finding that is partly in contrast to others,¹¹ who showed a clear reduction in intellectual function with lengthening time after 18 Gy of CRT in childhood ALL patients. However, in 80% of the children this decline appeared 4 to 8.5 years after diagnosis, indicating that extrapolation outside this range would be an over interpretation of that data. Thus, the present study is the first to show no further decline in neuropsychological capacity in the period 8 to 27 years after CRT.

In some studies,^{2,7} but not all,⁹ girls have shown more impairment of verbal IQ and of global depression of cognitive functioning after CRT and MTX¹⁰ compared to boys. It has been speculated that global deficits might be associated with diffuse

axonal injury, a neurotoxicity that might be both endocrine dependent and worsened by large doses of chemotherapy.⁵⁹ The present study, which included an equal proportion of women and men with former CO ALL, showed no gender difference in neuropsychological functioning in adulthood. The men and women in the present study were well-matched for percentage that had been treated with CRT up to age 6 years, age at diagnosis and at CRT, the target doses of CRT and risk group classification.

GH status has not been taken into account in relation to neuropsychological outcome in previous studies of former CO ALL patients.^{2,4} In the present study, treatment with GH for one year did not yield any improvement in neuropsychological test scores, compared with changes in the controls. One explanation might be that irreversible brain damage had been caused by CRT and/or chemotherapy in childhood. Moreover, the lack of GH and/or IGF-I during brain development could result in deficient neuronal and glial growth or suboptimal myelinisation,⁶⁰ which may not be reversible later in life. While development of cortical grey matter peaks at approximately four years of age, cortical white matter volume increases continuously until age 20 years⁶¹ and even slight pathology of white matter has been associated with distinct attentional dysfunction.⁶² Low levels of GH/IGF-I have been shown to parallel a reduction in attention-related brain potential from EEG traces.⁶³ However, contrary to this hypothesis of irreversible brain damage due to GHD, adults with CO GHD have shown improvements in cognitive function with GH treatment.⁶⁴ Further, in experimental studies peripheral infusion of IGF-I induced neurogenesis selectively in the adult rat hippocampus, a part of the brain connected with memory.⁶⁵

Another possible explanation for the lack of improvement after one year of GH is that the treatment period was too short to elicit a beneficial effect. However, Oertel *et al.*⁶⁶ found that GH substitution to adult onset GHD patients induced an improvement of attentional performance after only 3-6 months of GH treatment, and an improvement in cognitive function was also recorded in patients with Sheehan's syndrome and GHD after 6 months of GH treatment.¹⁹ In adult men with CO GHD, an improvement in memory function was recorded after one year of GH treatment.⁶¹ Different background diagnosis, age at diagnosis and whether CRT is the cause of GHD or not may explain differing results.

In conclusion, young adults with ALL in childhood treated by CRT and chemotherapy, and with confirmed GHD or insufficiency, had impaired neuropsychological performance but no difference in self-reported quality of life compared to matched population controls. One year of GH treatment did not improve scores in neuropsychological tests, which might either reflect irreversible damage to the brain, caused by CRT *per se* or by irradiation-induced GHD, or that the GH-treatment period was too short in this group of patients. This study again emphasises the importance of identifying the specific deficits in these patients and providing adequate support and training programs at an early age, together with educational support later in life. The effect of treatment with GH in this patient group has to be further elucidated and we need to understand whether GH ought to be introduced at a young age to perhaps counteract the cognitive impairment sequelae.

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Table 1. Symptom checklist (SCL)-90 scores of mental distress in 44 former ALL patients compared to 44 matched controls.

	Patients Median	25 th -75 th percentiles	Controls Median	25 th -75 th percentiles	P-value
Global severity index	0.22	0.16-0.51	0.33	0.13-0.65	0.49
Somatization	0.29	0.17-0.71	0.25	0.08	0.71
Anxiety	0.10	0.10-0.30	0.20	0.05-0.65	0.14
Interpersonal sensitivity	0.22	0.11-0.56	0.22	0.11-0.67	0.34
Depression	0.23	0.15-0.69	0.38	0.04-0.92	0.74
Obsession-Compulsion	0.40	0.26-0.90	0.50	0.10-1.05	0.81
Hostility-irritability	0.17	0.00-0.50	0.17	0.00-0.50	0.55
Phobic anxiety	0.00	0.00-0.21	0.00	0.00-0.21	0.41
Paranoid ideation	0.00	0.00-0.50	0.17	0.00-0.33	0.87
Psychoticism	0.00	0.00-0.30	0.10	0.00-0.20	0.21

Table 2. Neuropsychological test scores of 44 former ALL patients and matched controls.

	Patients (n=44)		Controls (n=44)		<i>P-value</i>
	Median	percentiles 10 th -90 th	Median	percentiles 10 th -90	
SRB:1 vocabulary	17.0	6.0 - 24.0	24.0	14.0 - 27.5	<0.001
WAIS-R Information	18.0	10.0 - 25.0	22.0	16.5 - 26.0	0.001
WAIS-R Block Design *	29.0	10.4 - 40.0	37.0	22.4 - 47.6	<0.001 *
WAIS-R Digit Symbol	48.0	34.0 - 63.0	62.5	50.5 - 80.0	<0.001
Cronholm-Molander verbal memory, immediate recall *	20.0	15.0 - 25.0	24.0	15.2 - 28.0	0.009 *
-- , delayed recall *	17.0	11.0 - 23.0	22.0	12.4 - 27.0	0.006 *
Austin Maze, total errors	42.5	14.0 - 106.5	33.5	8.5 - 77.5	0.07
-- , total performance time (s)	206	142 - 388	159	92 - 371	0.018
APT Two-way RT, level (ms)	340	278 - 435	287	254 - 356	<0.001
-- , variation (ms)	71	48 - 107	55	39 - 78	0.001
APT Inhibition RT, level (ms)	425	331 - 620	383	311 - 467	<0.001
-- , variation (ms)	102	53 - 194	76	45 - 141	0.008
-- , failed inhibition ratio (%)	8.0	0 - 16.0	4.0	0 - 14.0	0.7
APT k-test, d'	4.0	3.0 - 4.5	4.2	3.6 - 4.6	0.10
-- , β	-0.83	-1.92 - -0.16	-0.64	-1.83 - 0.08	0.4
-- , RT level for correct responses, left part of screen (ms)	1137	858 - 1427	957	826 - 1170	0.001
-- , RT level for correct responses, center part of screen (ms)	944	697 - 1119	829	647 - 1095	0.014
-- , RT level for correct responses, right part of screen (ms)	1187	826 - 1683	1032	768 - 1227	0.001
-- , search strategy	0.57	0.48 - 0.71	0.56	0.46 - 0.68	0.2
-- , error ratio (%)	2.7	0 - 9.4	1.5	0 - 5.6	0.3

* Comparison based on 43 pairs (n=86). One patient did not show satisfactory cooperation during testing with the WAIS-R Block Design, and another patient did not cooperate satisfactorily in the Cronholm-Molander test.

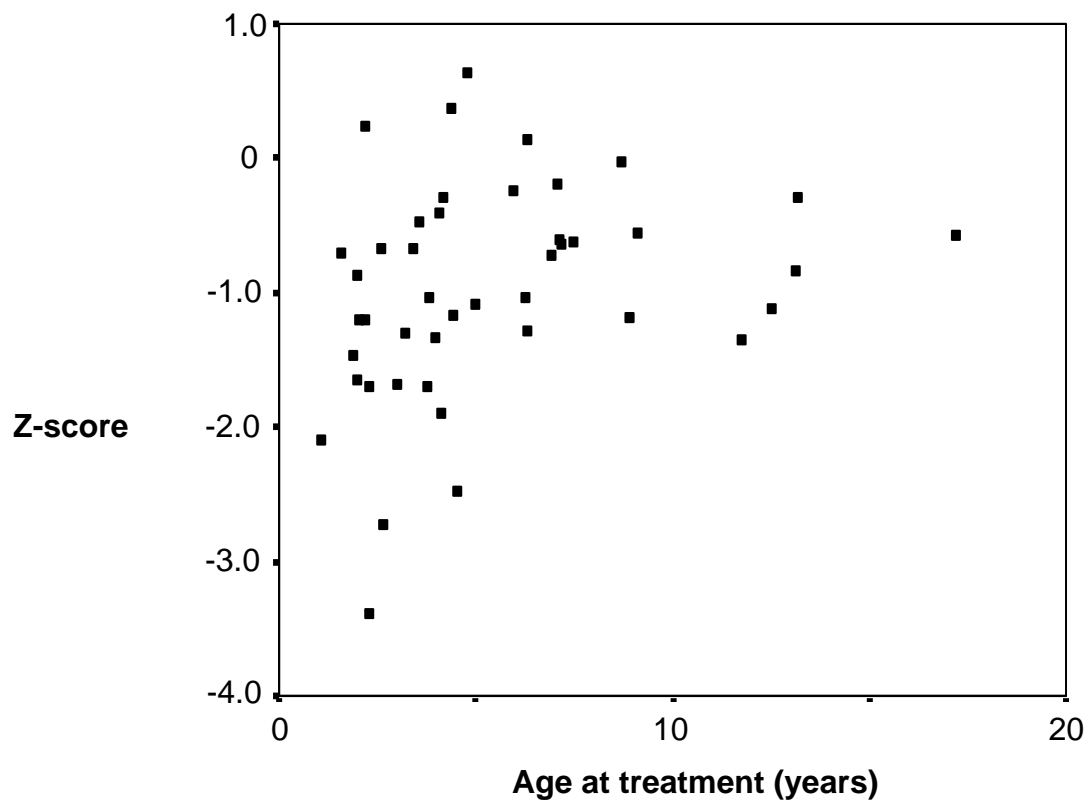


Figure 1. Mean performance level (Z-score) across all nine neuropsychological tests for the 44 ALL patients in relation to age at treatment.