Neuropsychological and Neurophysiological Functioning in Long Term Survivors of Acute Lymphoblastic Leukemia

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Abstract:

Acute leukemia's account for approximately 30% of malignancies occurring in childhood, However, 75% of those children were expected to survive. A major consideration in developing treatment protocols is to limit long-term effects of both the disease and therapy. This has led us to study the effects of different types of treatment on cognitive abilities. The sample was composed of 30 children with acute Lymphoblastic leukemia (ALL) who were divided into two groups according to the type of therapy, the first group received chemotherapy and the second group received chemotherapy and cranial irradiation. All of these groups were matched to a control group for age, sex & socioeconomic levels. Neuropsychological assessment were made using WISC-R for verbal (similarities), performance (block design) & short memory tests (digit span). Neurophysiological functioning was determined by means of EEG & P 300. We found cognitive deficit in acute leukemia survivors, mainly related to cranial irradiation in high doses directed to younger age patients (less than 5 years). These children may need special skill training to improve their educational outcome.

Introduction:

Among the childhood cancers, the acute leukemias are the most common. Accounting for approximately 30% of all newly diagnosed cases ***(Pui, 1997)*** Acute Lymphoblastic leukemia (ALL) is the most common acute leukemia in pediatric age group, accounting for approximately 80% ***(khalefa et al, 1999).***

Over the past thirty years, the use of presymptomatic central nervous system directed radiotherapy and chemotherapy for the treatment of childhood leukemia has reduced the incidence of central nervous system relapse and contributed to a steady increase in long term survivors ***(Chessels et al, 1992).*** As more children survive, however it became apparent that a significant number suffer from late side effects of treatment ***(Marina, 1997).*** These adverse effects include growth and endocrine dysfunction ***(Sklar, 1997)***, brain abnormalities such as calcification and white matter changes ***(Wilson et al, 1991),*** and cognitive impairment commonly manifested as lowered intelligence (IQ) and memory capacity ***(Waber et al, 1995)*** the brain pathology has been attributed to biochemical abnormalities resulting from both radiotherapy and chemotherapy ***(Hopewell, 1998, Ochs et al, 1991).*** This evidence has led to reduction of total dose of radiotherapy, increasing the number of fractionations in which the total cranial radiotherapy dose is given, avoidance of cranial radiotherapy in children less than two years, and limitation of prophylactic cranial radiotherapy to high risk groups ***(Christie et al, 1995).***

Objectives:

The present study was conducted in the pediatric hematology / oncology unit – Ain Shams University. The aim was to study the neurocognitive functions in survivors of childhood acute leukemia by

means of neuropsychological and neurophysiological l tests .The impact of various risk factors on neurocognitive functions will be assessed, including type and dose of radiotherapy and chemotherapy as well as other factors as sex, age or diagnosis, age at cranial radiotherapy and duration since radiotherapy.

Subject and Method:

The present study is a cross sectional study conducted in the Hematology-Oncology Unit, Children's hospital, Ain Shams University, in the period May-December 1998.

Patients Groups:

They included 30 patients with diagnosis of childhood acute Lymphoblastic leukemia (ALL), diagnosed in the period 1980-1992, who completed therapy and were off therapy in continuous complete remission. None of them had previous central nervous system relapse.

The ALL patients were subdivided into two groups according to the protocols of CNS prophylaxis received (table 1)

Group I:

It included 12 patients who received no cranial radiotherapy (Cr RT). CNS prophylaxis was given as combined intrathecal methotrexate, Ara C and hydrocortisone. Their age ranged between 6-19 years (mean 13.7 ± 3.9).They included 4 males and 8 females (M: F ratio of 1:2).

Group II:

It included 18 patients who received CNS prophylaxis cranial radiotherapy combined with intrathecal chemotherapy (methotrexate only in 4 patients and triple therapy with methotrexate Ara C and hydrocortisone in 14 patients).

Cranial radiotherapy was given in dose of 2400 C GY in 12 patients and 1800 c GY in 6 patients. The age range varied between 7-20 years at evaluation (mean 14.6 ± 4.8 years). They were 13 males and 5 females. (M : F ratio 2.6:1).

Control group

It included 30 healthy subjects, aged 6-20 years (mean 15.2 ± 8.3 years), including 16males and 14 females (M:F ratio 1.4 :1).All the included patients and controls were subjected to full medical, neurological and psychiatric history as well as thorough clinical and neurological examination comorbidity that might interfere with neurocognitive function results, was excluded. The included patients were subjected to the following investigations to ensure the maintained remission status and to exclude significant co-morbidity: complete blood count, cytological examination of bone marrow aspirate, lumbar puncture and cytological CSF examination, liver function test as ALT, AST and renal function tests including blood urea nitrogen and serum creatinine.

All the patients and controls were subjected for the following neuropsychological methods. I Q testing using Wechsler intelligence scale for children – revised (WISC-R), the subscales for verbal (similarities), performance (block design) & Memory tests (digit span) (Wechsler, 1981).Electroencephalography (EEG): to detect epileptic activity or background changes. Long latency auditory evoked potential (P_{300}) to detect problems in attention using ground electrode and active electrode placed as Cz and 2 reference electrodes at A_1,A_2. The patient sitting calm in quiet room is asked to

differentiate between 2 different frequencies in sound given in both ears.

Statistical analysis was done using student 't' test and chi-square by means of microstate computerized program.

$P<0.05$ is considered significant.

$P>0.05$ is considered insignificant.

$P<0.01$ is considered highly significant.

Results:

The age at evaluation varied between 6-25 years (mean 13.4 ± 7.5 years) with non significant difference between both groups of acute leukemia survivors and controls. The results of the present study are demonstrated in tables' (1) to (6) and in figure (1) and (2).

Table (1) demonstrates the demographic and clinical characteristics of the patients and controls. The age at diagnosis varied between 3-17 years with mean value of 8.4 years ±3.8 years & non-significant difference between both groups. A higher female ratio was observed in survivors who did not receive cranial irradiation prophylaxis (M:F is 1:2)

The duration of therapy varied between 3 – 6 years, (mean 4.5 ± 2.3 years) with significant longer duration in the patients who were planned for prophylactic cranial irradiation ($P<0.05$). Although non significant difference was observed between both groups as regards the cumulative oral methotrexate dose ($P>0.05$). The acute leukemia patients who received prophylactic higher dose of intrathecal chemotherapy (calculated as methotrexate dose / M^2 body surface areas), $P<0.01$. A history of convulsions was reported in 3/30 patients, including 2/18 who received cranial irradiation (convulsions developed 6 month and 19 weeks after cranial irradiation, respectively).

The results of IQ testing (Revised Wechler Scale) are demonstrated in table (2).

From this table it is evident that acute leukemia survivors did not differ significantly from healthy controls as regard verbal IQ ($P>0.05$). The performance IQ was significantly lower in leukemia survivors than controls ($P<0.05$). Assessment of short-term memory and attention by digit span test revealed significantly lower score in leukemia survivors ($P<0.01$).

Comparison of the results of long latency evoked potential in-patients and controls (table 3), revealed non-significant difference in p_{300} amplitude. The p_{300} latency was significantly prolonged in acute leukemia survivors' (P0.001).

EEG studies of acute leukemia survivors (table 4) revealed 9/30 (30%) patients had focal epileptiform discharge, compared to none in controls ($P<0.01$). None of these patients with focal discharge on EEG had history of convulsions and all were neurologically free. Among the three patients who gave past history of convulsions, all had normal EEG findings, None was on anticonvulsant therapy.

Comparison of the variable parameters of neurocognitive functions in acute leukemia survivors who received cranial (crRT) radiotherapy prophylaxis (1800 or 2400 c GY), those who had no cr RT and controls are demonstrated in table (5).

The verbal IQ was significantly lower in survivors who received crRT compared to controls ($P<0.01$), but the difference was not significant from those who did not have

cr RT.The performance IQ in patients with previous cr RT was significantly lower than controls (P<0.01) and survivors with no cr RT (P<0.01).The score of digit span as a measure of short term memory and attention was significantly lower in the cr RT group compared to controls (P<0.001).

Table (5) demonstrates that acute leukemia survivors who had cr RT did not significantly differ from the controls as regards verbal, performance IQ and attention studies.

Comparison of the latency of auditory event-related evoked potential in both groups of leukemia survivors, revealed significantly longer latency in patients who received Cr RT compared to controls (P<0.001) and survivors not receiving Cr RT (P<0.001), there was no significant difference between survivors without Cr RT and controls.

Focal epileptiform discharge on EEG was observed in 5/12 (41.7%) of survivors with no Cr RT, the incidence being significantly higher in both groups compared to controls (P<0.001), with insignificant difference between both groups.

Considering the effect of the dose of cranial radiotherapy on neurocognitive functions in (table 6), revealed that a dose of 2400 cGY was associated with significantly lower performance IQ, attention score and P_{300} latency when compared to patients who did not receive cr RT (P<0.001). However, Cr RT in dose of 1800 c GY was not associated with significant difference in IQ parameters compared to no Cr RT group (P>0.05). The P_{300} latency was significantly longer in the 1800 c GY group compared to patients who did not receive cr RT (P<0.001), denoting underlying cognitive dysfunction. EEG changes did not differ significantly in relation to cranial radiotherapy.

Figure (1) demonstrates that acute leukemia patients who received prophylaetic cr RT or below five years of age had lower scores in performance IQ and attention scores compared to older age, however the difference was not statistically significant (P>0.05). There was no significant difference in the P_{300} latency and EEG abnormality and age at cr RT.

Figure (2) illustrates the difference in the cognitive parameters in relation to prophylactic cranial irradiation.In the non irradiation group, females had significantly lower verbal IQ and attention scores compared to males (P<0.05). In the group who received cr RT, females had lower scores compared to males in all the studied IQ parameters, however the difference was not statistically significant. There was no significant sex difference between patients as regards P_{300} latency and EEG abnormalities.

In the present study, there was no correlation between the IQ parameters, P_{300} latency and abnormal EEG and the following parameters studied: age of evaluation, duration of therapy, duration since stoppage of therapy, duration since cranial radiotherapy, cumulative dose of oral methotrexate or cumulative dose of intrathecal methotrexate.

Table (1): Demographic and clinical characteristic of patients groups and controls.

Variable	Group I	Group II	Controls
	No cr RT n = 12	Prophylactic Cr RT n = 18	No = 30
Age of evaluation (years) ± Range (mean + SD)	6-19 (13.7 ± 3.9)	(7-20) 14.6 ± 4.8	(6-20) 15.25 ± 8.3
Age at diagnosis (years) Range (mean + SD)	(3-15) 9 ± 4.3	(4-14) 8.1 ± 2.9	-
Sex [M / F ratio]	4 / 8	13 / 5	16 / 14
Duration of therapy (years) Range (means +SD)	(2-3) 2.7 ± 0.3*	(2-6) 3.7 ± 0.6	-
Dose of Cr. RT	-	2400 CG: n = 12 1800 CG: n = 6	-
Cumulative oral MTX/M^2 Range (mean ± SD)	(900 – 4500) 1672 ± 1052	(970 – 4900) 2112 ± 794	-
Cumulative II MTX/M^2 Range (mean ± SD)	(100-214) 138 ± 54**	(110 – 380) 204 ± 65	-
History of convulsions	1 (8.3%)	2(11.1%)	-

Test of significant: student's t test

* $P < 0.05$ significant

** $P < 0.01$ highly significant.

N.B none of the patients studied received intermediate or high dose intravenous methotrexate.

Table (2): Comparison of results of I Q testing in acute leukemia survivors versus controls

I Q Test / Groups	"Similarities" Verbal IQ M ± SD	"Block Design" performance IQ M ± SD	"Digit Span" M± SD
Patients n = 30	10.18 ± 3.4	8.00 ± 2.5	8.40 ± 2.1
Controls n = 30	13.03 ± 3.0	9.60 ± 2.2	10.2 ± 2.1
T values	T = 1.171	T = 2.632	T = 3.321
P value	P > 0.05 (NS)	P < 0.05 (S)	P < 0.01 (H.S)

Scores above 6 out of 10 were considered normal in each of the (subscales of WISC-R)

Table (3): Comparison of results of long latency evoked potentials (P300) in patients and controls:

P300	Patients (n=30) M± SD	Controls (n=30) M ± SD	t	P
Latency (msec)	(313.9 ± 38.5)	239 ± 45.6	6.874	<0.00 1
Amplitude (uv)	4.8 ± 3.3	4.5 ± 3.5	0.375	>0.05

Test of statistical significance used is the unpaired student's t-test
P<0.01 very highly significant
P>0.05 N.S

Table (4) : Comparison of EEG findings in survivors of acute leukemia compared to controls.

	Patients N=30 N (%)	Controls N=30 N (%)	P-Value
Normal	18 (60%)	26 (86.7%)	
Focal epileptiform discharge	9 (30%)	Zero (0%)	(P<0.01)
Theta dysrythmia	3 (10%)	4 (13.3%)	

The test of statistical significance used is the chi Square test.

Table (5) Comparison of the different groups as regards variable parameters of neurocognitive function

	Group I N=12	**Group II N=18**	**Controls N=30**
V IQ (M±SD)	(12.2 ± 2.4)	(10.1 ± 1.3)	(13.03 ± 3.0)
P IQ (M±SD)	(10.2 ± 1.5)	(7.2 ± 2.6)	(9.6 ± 2.2)
Memory tests (M±SD)	(9.4 ± 1.3)	(7.25 ± 1.2) *	(0.2 ± 2.)
P300 latency (msec)	(231.33 ± 42.5)	(334.9 ± 37.7) **	(239.6 ± 45.6)
Abnormal EEG (focal disorder) N (%)	5(41.7%)x	4 (22.2%)	- zero %

* P < 0.01 ** P < 0.001
P < 0.01 P < 0.001
x P < 0.001
group I : No cranial irradiation
group II : prophylactic cranial irradiation.

Table (6): Dose of prophylactic cranial radiotherapy as risk factor for neurocognitive dysfunction in acute leukemia survivors.

	Cr RT 2400 cgy n=12	Cr RT 1800 cGY n=6	No cr RT n=12
Verbal IQ (mean ± SD)	11.08 ± 2.7	13.3 ± 0.5	12.2 ± 2.4
Performance IQ (mean ± D)	7.42 ± 1.8*x	10.3 ± 3.9	10.2 ± 1.5
Short term memory (mean ± SD)	7.25 ± 1.3*	8.3 ± 4.1	9.4 ± 1.3
P300 latency (msec) M ±SD	313.8 ± 23.4*	318.0 ± 13.9*	231.3 ± 42.5
Abnormal EEG	3 (25%)	2 (33.3%)	14 (33.3%)

*P < 0.001 (t test: compared to no cr RT group)
x P < 0.05 (t test: 2400 cGY compared to 1800 cGY)

Fig I: Age at prophylactic cranial radiotherapy as risk factor for cognitive dysfunction in survivors of childhood acute Lymphoblastic leukemia.

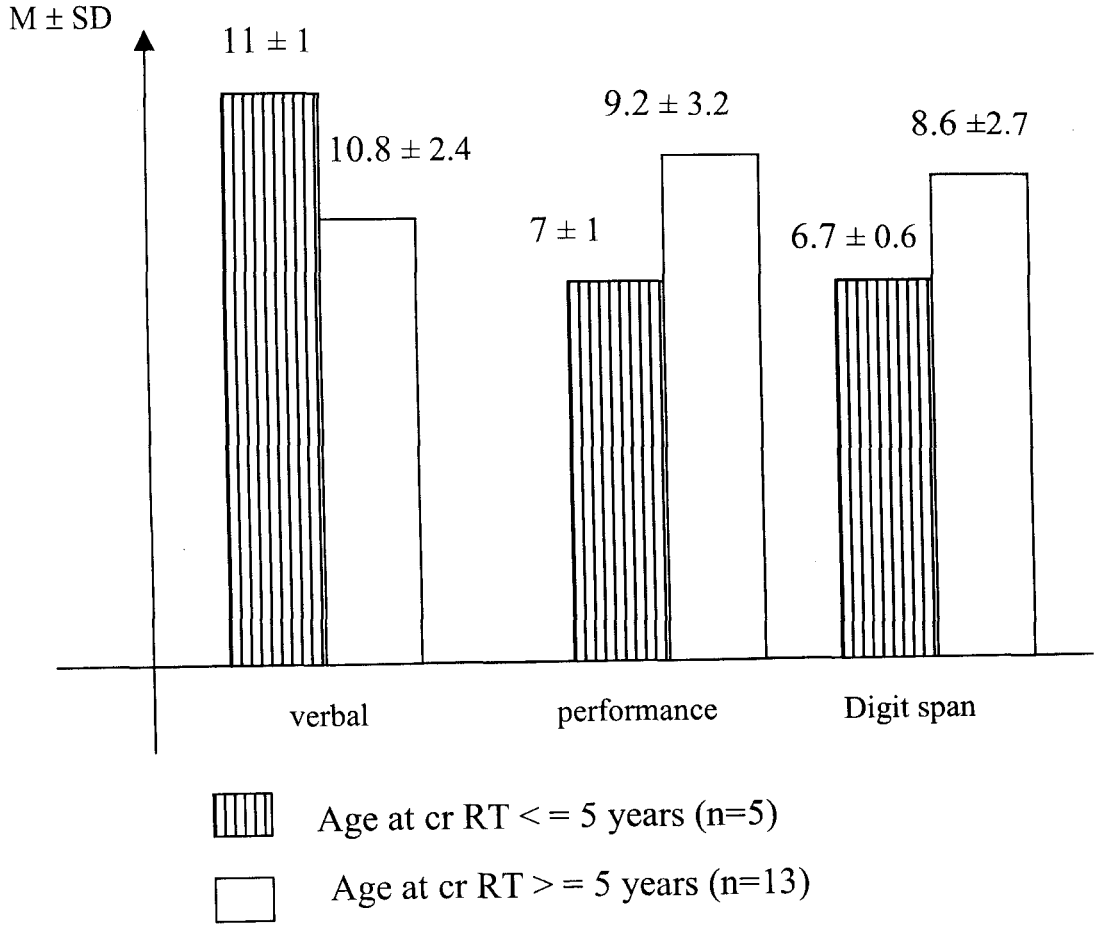
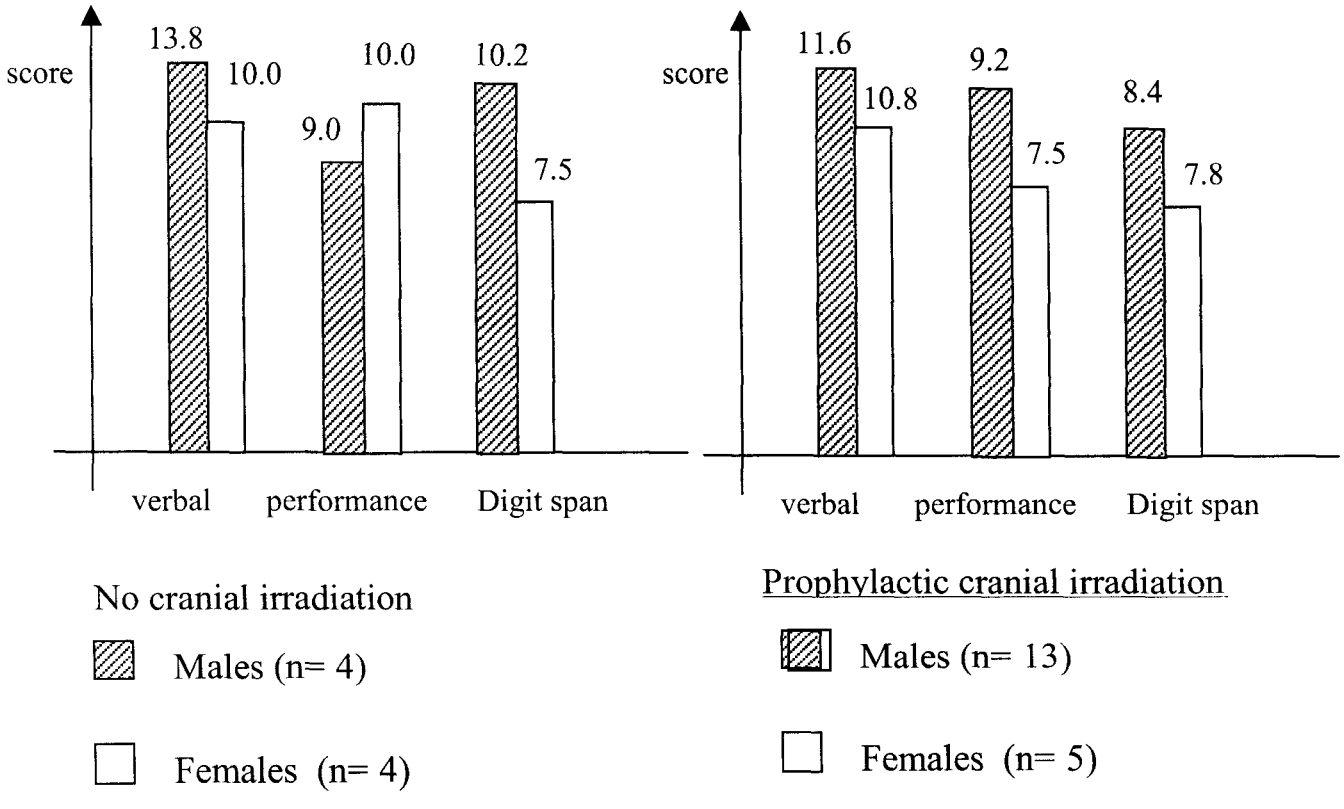


Fig (2) : Sex as risk factor for cognitive dysfunction in survivors of childhood acute Lymphoblastic leukemia.



Discussion

The present study explored the association of treatment and patient- related factors with neuropsychologic tonicities among thirty survivors of childhood acute lymphoblastic leukemia attending the Hematology. Oncology unit, Children's Hospital Ain shams University.

The results of the present study revealed that acute leukemia patients who received chemotherapy alone did not differ significantly from healthy controls as regards verbal IQ, Performance IQ as well as short term memory (digit span) and auditory attention tests (P_{300}) latency. All these parameters were significantly impaired in ALL patients who received crRT compared to controls.

These finding confirm and extend previous reports of reductions in intellectual abilities after presymptomatic cranial irradiation ***(Smibert et al 1996. Christe et al 1995, Moss et al 1981. Copeland et al, 1985, Rowland et al, 1984. Meadows et al, 1981).*** However, ***(Ochs et al 1991)*** and others ***(Ivnik et al, 1981 ,Whitt et al 1984, Ochs et al, 1991)*** failed to demonstrate IQ differences in irradiated acute leukemia patients in both retrospective and prospective studies.

(Smibert et al 1996) reported that the intellectual deficit associated with cranial irradiation is relatively mild, with mean scores of performance and verbal IQ within the average range a defined by Wechsler scale.

This statement is in accordance with our findings. This may explain why some studies have failed to detect intellectual deficits with cranial irradiation. When the irradiated patients were compared to non irradiated groups, the intellectual deficit pattern revealed that differences in verbal IQ were minimal and non significant, however differences were highly significant as regards short term memory and attention (P_{300} latency), next followed by performance IQ. These results concerning minimal verbal IQ changes and more prominent performance IQ deterioration coincide with.(***Abdel Baky et al 1997).***

However, other studies demonstrate more affection in verbal skills in association with cranial irradiation ***(Berta 1994, Smibert et al, 1996 Christi et al, 1995, Ochs et al, 1991).***

The findings of the present study concerning significant alternations of short term memory (digit span) and auditory attention (P_{300} latency), coincide with other reports ***(Abdel Baky, et al 1997, Whitt et al, 1984, Cousens et al, 1991).***

(Dennis et al 1998), found that children irradiated for brain tumors experienced deterioration in parameters of attention and memory.

Regarding the dose of prophylactic cranial radiotherapy a dose of 2400 CGY was associated with significant decrease in performance IQ, relative decrease in short term memory and non significant change in verbal IQ when compared to patients receiving 1800 c GY Patients. The 1800 CGY group did not differ significantly from non irradiated patients in verbal IQ, performance IQ and short term memory. However the P_{300} latency denoting defective attention and subclinical brain damage (Uberall et al, 1996) was significantly longer in both cr RT groups compared to non irradiated group.These results coincide with previous reports (Halberg, et al, 1991, Smibert et al 1996, Hopewell 1998).P300 latency was affected more than the amplitude. This may indicate that the underlying pathological changes are probably demyelinative rather than axonal , and this type of pathology is regressive with proper remyelination.

That high dose cr RT (2400 cGY or more) is associated with more adverse effects with regards to intellectual and educational abilities. Neuroimaging studies have supported these findings identifying more significant changes in the CNS white matter after high dose cr RT ***(Hopewell 1998, Hertzberg et al 1997, Browners and Poplack, 1990).***

However, although we found greater adverse effects with high dose (2400 cGY) cr RT, children who received 1800 cGY cr RT did not perform as well as the controls especially concerning digit span ($.3 \pm 4.1$ vs10.2 ± 2.1) reflecting defective short term memory, as well as the p_{300} latency which was prolonged significantly compared to non irradiated leukemia patients and controls. The p_{300} measurement is useful as objective measure of the cognitive process, delayed latency reflects subclinical neuronal dysfunction.

Finding support ***(Jankovic et al 1994 & Smibert et al 1996)*** that demonstrated the relative effects on neurocognitive functions using 1800 cGy cr Rt.

On the other hand, studies done by ***(Mulhern et al 1991)*** and others ***(Ivnik et al, 1981, Whitt et al 1984)*** reported that no greater deficit in neuropsychological dysfunction were observed with cr RT than with parental MTX alone and no differences between 1800 cGY and 2400 cGY as irradiation.

Chronological age of the patient at the time of cranial radiotherapy has been considered as a critical factor for outcome ***(Smibert et al, 1996).***

In the present study, comparison of IQ parameters in patients aged at time of cr RT 5 years or less to patients older than 5 years revealed no difference in verbal IQ (11 ± 1), lower performance IQ (7 ± 1 vs 9.2 ± 3.2) and lower digit span score (6.7 ± 0.6 vs 8.6 ± 2.7).

However, the difference was not statistically significant possibly related to the small numbers of patients in the group <= 5 years (n=5). Similarly other studies ***(Christie et al 1995, Cousens et al 1991, Abdel Bakey, et al, 1997, Kato et al,1993)*** revealed that irradiation at younger age especially between five years adversely affects intellectual and educational achievements with greater problems occurring for non verbal skills as well as in measures of short term memory and attention. The effect of age at treatment may be related to age dependent myelination rates in the developing central nervous system ***(Christie et al, 1995).*** As different anatomical regions (and therefore functional systems) myelinate at different times there may be a differential response to neurotoxins as function of age and stage of brain development. ***(Hopewell, 1998).***

However, other studies ***(Longeway et al, 1990)*** reported no age related differences in the intellectual functions of leukemia survivors related to cr RT Although there is a consensus that intellectual ability declines over time after cranial irradiation and central nervous system chemotherapy ***(Dowell et al 1991)***, no significant correlation was found in the present study between the duration since CNS prophylaxis and the various cognitive parameters. Similar absence of significant correlation was reported by other studies ***(Christie et al 1995, Smibert et al 1996, Longeway et al 1990).***

As regards sex as risk factor for cognitive dysfunction in all survivors, the present study revealed that in the non-irradiation ALL both verbal IQ and digit span (short term memory and attention) were significantly lower in females compared to males. In the group who received cr. RT., females had lower scores in verbal IQ, performance IQ and digit span than males, however, not statistically significant. In many studies, females are considered to be at greater risk than males for intellectual deficits, especially verbal IQ and other aspects of verbal ability, following treatment for acute lymhoblastic leukemia (Waber et al 1992, Waber et al, 1995, Christie et al 1995). Females may also display a group at risk of neuroendocrine and growth abnormalities after cr. RT. The mechanism responsible for their differential vulnerabilities is still undefined. ***(Bleyer, 1998 and Waber et al, 1990)*** believed that sex differences were indicative of a fundamental interaction between postnatal neural development and other biologic process.

However, the sex difference in cognitive dysfunction in all survivors was not supported by the study of ***(Smibert et al 1996).***

Intrathecal methotrexate has been documented as causing CNS damage ***(Waber et al, 1995).*** The present study shows that, systemic chemotherapy plus intrathecal methotrexate (alone or with ara C and hydrocortisone) without cranial irradiation did not affect the mean value of intellectual capacities, similar results were reported by ***(Copeland, et al 1996, Christie et al 1995).***

On the other hand, studying of individual patients revealed that marked deviations in digit span scores (attention and short term memory) were observed in 2/12 (16.6 %) of non irradiation compared to 5/18 (27.75) of the studied irradiation patients. Similarly. Ochs et al (1991) reported intellectual changes with chemotherapy, although less than with cr RT. They reported high frequencies 20% of transient white matter hypodensity .It has been reported that when cranial irradiation was given to children who received chemotherapy and intrathecal methotrexate, the cognitive and academic abilities are adversely affected. It may be that the intrathecal chemotherapy renders the brain more susceptible to cr RT damage ***(Hopewell 1998, Bleyer 1998).***

In the present study, EEG abnormalities focal discharge were observed in 5/12 (41.7%) of non irradiated patients and 4/18 (22.2%) of the irradiated group, this finding was significantly higher than in the controls. There was no correlation between the EEG findings, history of seizures, and often-intellectual parameters as IQ & P300 values. Focal EEG abnormalities found in group I and not in group II indicate that intrathecal chemotherapy has some cerebral injurious side effects, thus chemotherapy cannot be considered totally safe compared to cranial irradiation alone. This finding coincides with ***(Ochs et al 1991)*** who reported abnormal EEG in 61% ALL survivors who received only chemotherapy including seizure discharge in 25 %, compared to abnormal EEG in 34% of cr RT group, none having focal discharge. They explained the EEG abnormalities in the chemotherapy group to be related to possible methotrexate interference with neurotransmitter synthesis, release or degradation over prolonged periods of time.

On the other hand, history of seizures was reported in 3/30 patients in the present study (10%) (2 irradiated and non-irradiated), compared to incidence of 8% in ***(Ochs et al 1991)*** study. In both studies, no abnormal EEG was found in relation to history of seizures. This inability of EEG assessment to predict clinical seizures is disappointing ***(Ochs et al, 1991).***EEG abnormalities were found in patients having no history of convulsions as the abnormalities may be non epileptogenic (diffuse theta dysrhythmia)or may be subictal discharge (focal epileptogenic discharge) that could not produce convulsive attacks but cognitive or mental symptoms.

In the last few years, cranial radiotherapy has been limited to high risk ALL patients and replaced by intermediate or high dose intravenous methotrexate therapy. ***(Whitlock & Gaynon 1999).***

However, ***(Ochs et al 1991)*** reported that cr RT dose reduction that are accompanied by increase in intrathecal and / or parental methotrexate may not necessary reduce long term neuropsychological toxicities. The toxicity of various CNS prophylaxis regimens should be interpreted in the context of the potential cumulative toxicity of the earlier therapy plans. Similar results were obtained by ***(Waber et al, 1995)***

In conclusion, the present study demonstrates cognitive impairment in acute leukemia survivors, mainly related to cranial irradiation, although some studies suggested the role of environmental, social factors and school absence ***(Smibert et al, 1996).*** Some specific risk factors have been identified in relation to intellectual functions. High dose cranial radiotherapy (>= 2400 Cgy) is a significant risk factor related to generalized damping of abilities. Treatment before five years of age is related to poorer intellectual ability, although more studies are needed in the young age (<= 2 years) for neurotoxicity of chemotherapy. Dose of 1800 cGY cranial irradiation in a child older than five years do not appear to be detrimental to intellectual ability. Finally, it should be emphasized that the pattern of deficits exhibited by children receiving cr RT is generally suggestive of mild impairment of intellectual abilities, but may have serious impact on educational skills. These children may benefit from special assistance to improve their educational outcome. This is important in order to improve the quality of life of survivors of ALL to help them achieve their maximum potential, at school and in the work force.

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الوظائف الفسيولوجية و السلوكية في مرضى اللوكيميا الليمفاوية

يعتبر سرطان الدم من اكثر انواع الامراض الخبيثة انتشارا في الاطفال و يستجيب حوالى ٧٥% من المرضى للعلاج و من الامور الهامة في تحديد برنامج العلاج و دراسة الاثار الجانبية للمرض و الاساليب المختلفة للعلاج

في هذا البحث قمنا بدراسة ٣٠ طفل يعانون من سرطان الدم و تم تقسيم العينة إلى مجموعتين الاولى تعالج بالأدوية الكيماوية و الثانية يعالجون بالأدوية الكيماوية و الإشعاع على خلايا المخ و تم مقارنة هذه العينة بمجموعة ضابطة من حيث الوظائف العليا للمخ باستخدام اختبار وكسلر و رسم المخ و الموجات المستفزة للمخ ووجد ان وظائف المخ تتأثر في الأطفال الصغار في السن (اقل من خمس سنوات) في الحالات التي تم علاجها باستخدام الإشعاع على المخ

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24 hours emergency service.
Three daily outpatients clinics, four days a week.

Four specialized clinics in child psychiatry, addiction, psychosexual disorder, and sleep disorders.

An inpatient department with 100 beds, 25% of which are free .

A day hospital that provides rehabiliative, vocational and occupational therapies for patients with residual handicaps secondary to their mental disorders.

An electrophysiological unit embracing asssessment through EEG, evoked potential, brain map and sleep laboratory.

A unit for psychological assessment.

A biochemical laboratory which carries out routine lab investigations in addition to substance detection in body fluids.