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Assessment of Cognitive Function in Children with Acute Lymphoblastic Leukemia

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Abstract

The success in the treatment of acute lymphoblastic leukemia (ALL) has significantly contributed to the growing number of pediatric cancers survivors with long-term complications as impaired neurocognitive and psychological functioning. The aim of the present study was to assess the cognitive function in children with ALL. The study was conducted on 3 groups: The first group include 20 known ALL patients, receiving chemotherapy in the maintenance phase, the second group included 20 ALL survivors who had completed 3 years of chemotherapy and were off therapy at the time of the study and the third group included 20 healthy children of matching age and sex from the population or siblings of ALL patients as controls. Their age ranged from 5 to 15 years. They were subjected to thorough history taking, full clinical examination and laboratory investigations, and neuropsychological assessment using: Wechsler Intelligence Scale to assess cognitive function and socioeconomic status (SES) of the parents was assessed according to a scoring system modified after Fahmy and El Sherbiny. The results revealed that there was no significant difference between cognitive function of ALL children receiving treatment in the maintenance phase and the control group. While the leukemic children who had completed 3 years of treatment and were off therapy had a significantly lower cognitive function compared to ALL cases receiving treatment and to the control group. In conclusion, the cognitive function is not affected by the occurrence of ALL itself but it may show a progressive decline with ALL treatment.

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Introduction

The leukemia's may be defined as a group of malignant diseases in which genetic abnormalities in a hematopoietic cell give rise to an unregulated clonal proliferation of cells. The clinical features, laboratory findings, and responses to therapy vary depending on the type of leukemia [1]. Acute leukemia's constitute 97% of all childhood leukemia's and consist of the following types:

1) Acute lymphoblastic leukemia (ALL) – 75%

2) Acute myeloblastic leukemia (AML), also known as acute non-lymphocytic leukemia (ANLL) – 20%

3) Acute undifferentiated leukemia (AUL) – <0.5%

4) Acute mixed-lineage leukemia (AMLL) [2].

Acute leukemia is the most common malignant disease affecting children and accounting for nearly one third of childhood cancer [2].

The survival rate of childhood acute lymphoblastic leukemia (ALL), has improved in recent years to a 5-year survival rate of about 80%, although it is often less than 35% in developing countries. The long-term toxicity and functional outcome have become important in monitoring survivors of childhood leukemia because of this improvement in survival rate [3].

This improvement in survival rate made the long-term toxicity and functional outcome to become important in monitoring survivors of childhood leukemia [4], with part of this monitoring is the neuropsychological impact of childhood cancers and their treatment. The neuropsychological impact of childhood cancers and their treatment, can be divided into core and secondary symptoms: core deficits which involves executive functions, processing and fluent abilities and secondary deficits which includes broad spectrum abilities measured by tests of academic achievement and intellectual functioning. The neurobehavioral and cognitive squealae were relating to biologic factors, with disease and/or treatment related factors as mediators and

gender, age at diagnosis, time since diagnosis, age at testing and environmental factors such as socioeconomic and family status as moderators [5].

The aim of the present work was to assess the cognitive function in children with ALL during and after completion of chemotherapy.

Patients and Methods

Patients

The study was conducted at the Hematology-Oncology unit of Alexandria University Children's Hospital, Alexandria, Egypt on 60 children divided as follows:

Group (A): twenty known ALL patients, receiving chemotherapy in the maintenance phase, group (B): twenty children with ALL who received chemotherapy for 3 years and are off therapy now (they received the same treatment regimen as group A), and they were subdivided into group (B1): those who had received cranial irradiation as part of CNS prophylaxis and group (B2): those who did not receive cranial irradiation, group (C): twenty healthy children of matching age and sex from the population or siblings of patients with ALL as controls. Their ages ranged from 5 to 15 years. Cases with CNS infiltration and preexisting neurological or psychiatric conditions were excluded from the study.

A written informed consent was obtained from the guardians of all the participants. The study was approved by the ethical committee of the Faculty of Medicine Alexandria University.

Also the study procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 2000.

Methods

All the studied children were subjected to the following: Thorough history taking specifically developmental history. Complete clinical examination with special emphasis on: manifestations of acute leukemia and full neurological examination. Laboratory investigations including: complete blood count (CBC), bone marrow aspiration and CSF cytology and pathological examination: to exclude CNS leukemia or meningitis.

Cognitive assessment was tested using The Arabic Version of the Revised Wechsler Intelligence Scale for Children (for age range 5-15 years) [6]. It comprises 13 subsets, which are divided into assessment of verbal, and performance scales. The verbal intelligence quotient (IQ) reflects left-hemisphere functioning whereas the performance IQ reflects right–hemisphere functioning.

Socioeconomic status (SES) of the parents (occupation, level of education, income, family number, crowding index, and sanitation) was assessed according to a scoring system modified after Fahmy and El Sherbiny [7] and was classified into four levels: high, high middle, low middle, low.

Statistical Methods

Data were fed to the computer and analyzed using IBM Statistical package for social science for personal computers version 20.0.

Continuous variables are presented as mean ± standard deviation, whereas discrete variables are described using absolute and relative frequencies. Comparison between different groups regarding categorical variables was tested using Chi-square test. When more than 20% of the cells have expected count less than 5, correction for chi-square was conducted using Fisher's Exact test or Monte Carlo correction.

For normally distributed data, comparisons between two independent populations were done using independent t-test while more than two populations were analyzed F-test (ANOVA) to be used and Post Hoc test (Scheffe). Correlations between two quantitative variables were assessed using Pearson coefficient. For abnormally distributed data, comparison between two independent populations were done using Mann Whitney test while Kruskal Wallis test was used to compare between different groups.

Significance test results are quoted as two-tailed probabilities. Significance of the obtained results was judged at the 5% level.

Results

The age of the sixty studied children ranged from 5-15 years. There was no significant difference as regards age among the three studied groups p = 0.633). This is shown in **Table 1**.

Table 2 shows sex distribution among the 3 studied groups. Group A included 13 boys (65%) and 7 girls (35%); group B included 8 boys (40%) and 12 girls (60%) and group C included 10 boys (50%) and 10 girls (50%), with no significant difference between the three studied groups (p = 0.281).

All studied children had normal developmental history. Also there were no abnormal neurological findings by clinical examination in the three studied groups.

Table 3 shows a comparison of intelligence quotient (mean full scale IQ (FSIQ), verbal IQ, performance IQ scoring and their subscales) between the three studied groups. The mean FSIQ, verbal IQ (subscales: arithmetic, similarities and comprehension) and performance IQ (subscales: picture completion, mazes, geometric design and block design) were significantly lower in group B compared to group A and C. Otherwise, there was no significant difference as regards information, vocabulary, and object assembly among the 3 groups. Moreover, there was no significant difference in mean FSIQ, verbal IQ, performance IQ and their subscales between group A and group C.

Table 4 demonstrates a comparison of intelligence quotient (mean FSIQ, verbal IQ, performance IQ scoring and their subscales) between boys and girls in group A and group B. There was no statistically significant difference between boys and girls as regards mean FSIQ, verbal IQ, performance IQ and their subscales in neither group.

The comparison of intelligence quotient (mean FSIQ, verbal IQ, performance IQ scoring and their subscales) between different levels of SES: low, low middle, high middle in groups A & B showed no statistically significant difference.

Table 5 shows a comparison of intelligence quotient (mean FSIQ, verbal IQ, performance IQ scoring and their subscales) between

Table 1 Age at time of study for the three studied groups.

	Group A		Group B		Group C		p
	No	%	No	%	No	%	
Age							
5 - <8	10	50.0	6	30.0	6	30.0	p = 0.633
8 – 12	6	30.0	7	35.0	8	40.0	
13 - 15	4	20.0	7	35.0	6	30.0	
p_1			0.374		0.560		
p_2					0.931		
Min.-Max. age.	5.17 – 14.08		7.0 – 15.0		5.0 – 15.0		$^{F}p = 0.717$
Mean ± SD	8.87 ± 3.06		10.75 ± 3.04		9.70 ± 3.26		
$^{Sch}p_1$			0.172		0.702		
$^{Sch}p_2$					0.572		

χ^2: Chi square test
F: F test (ANOVA)
Sch: Post Hoc Test (Scheffe)
P: p value for comparing between the different studied groups.
p_1: p value for comparing between group A with group B and group A with group C.
p_2: p value for comparing between group B and C.

Table 2 Sex distribution for the three studied groups.

	Group A		Group B		Group C		p
	No	%	No	%	No	%	
SEX							
Male	13	65.0	8	40.0	10	50.0	p = 0.281
Female	7	35.0	12	60.0	10	50.0	
p_1			0.113		0.337		
p_2					0.525		

χ^2: Chi square test
F: F test (ANOVA)
P_1: p value for comparing between the different studied group with group C.
p_2: p value for comparing between group B and C

ALL survivors who completed 3 years of treatment who had received cranial irradiation as part of CNS prophylaxis group B1 and those who did not receive cranial irradiation group B2.

Group B1 had statistically significant lower intelligence quotient results as regards the mean FSIQ, verbal IQ (subscales: information, similarities and comprehension) and performance IQ (subscales: picture completion, mazes and block design) compared to group B2, ($p<0.001$).

Figure 1, **Figure 2** and **Figure 3** illustrate a positive correlation between the age at diagnosis (in years) and the FSIQ ($r=0.933$, $p<0.001$), the Verbal IQ ($r=0.894$, $p<0.001$) and Performance IQ ($r=0.838$, $p<0.001$) respectively in ALL children who completed 3 years of treatment (group B).

Discussion

The results of the present study showed that cognitive function (FSIQ, Verbal IQ, Performance IQ and their subscales) did not differ significantly between ALL children receiving treatment in the maintenance phase and the control group. This means that the disease itself and the earlier phase of treatment has no significant impact on the cognitive functions. Supporting our result, Kingma et al [8] showed no significant difference as regards cognitive functions between newly diagnosed leukemic children and control group.

The present study demonstrated that children who had completed 3 years course of treatment consistently experienced significant deficits in the neurocognitive function IQ (FSIQ, verbal IQ and performance IQ) compared to ALL cases still receiving the same treatment as group B and the control group. In addition, some subscales of verbal IQ (arithmetic, similarities and comprehension) and some subscales of performance IQ (picture completion, mazes, geometric design and block design) showed significant differences between these groups. Similarly, Anderson et al [9] and Dowell et al [10] suggested that children who had survived leukemia typically obtain lower IQ score than matching healthy children. Moreover, Campbell et al [11] found a decline in both global and specific areas of neurocognitive functioning as a result of contemporary ALL treatment. Also, a study done by Raymond et al [12] illustrated that the chemotherapy with or without cranial irradiation to leukemic children was associated with significantly lower levels of intellectual and academic function. Eberhardt et al [13] illustrated that there is significant cognitive impairments in verbal function after the initiation of treatment in cancer patients. Even, the patient with base - line cognitive function (after 5 ± 3 days from start of chemotherapy)

Table 3 Comparison of the intelligence quotient IQ between children with ALL under treatment (group A), children with ALL after 3 years of treatment completion (group B), and the control group (group C).

	Group A	Group B	Group C	p_1	p_2	p_3	p_4
Full scale IQ							
Min.-Max.	87.0 – 101.0	72.0 – 99.0	90.0 – 103.0	<0.001*	0.001*	0.672	<0.001*
Mean ± SD	95.45 ± 4.54	87.85 ± 8.03	97.10 ± 4.13				
Verbal IQ							
Min.-Max.	94.0 – 109.0	80.0 – 103.0	95.0 – 109.0	<0.001*	0.001*	0.882	<0.001*
Mean ± SD	99.15 ± 3.96	92.95 ± 6.79	99.95 ± 3.78				
Information							
Min.-Max.	9.0 – 15.0	8.0 – 16.0	9.0 – 15.0	0.722	0.956	0.882	0.727
Mean ± SD	11.10 ± 1.33	11.25 ± 1.94	10.85 ± 1.39				
Vocabulary							
Min.-Max.	9.0 – 16.0	9.0 – 13.0	9.0 – 17.0	0.706	0.953	0.711	0.875
Mean ± SD	11.35 ± 1.69	11.20 ± 1.06	10.95 ± 1.73				
Arithmetic							
Min.-Max.	6.0 – 12.0	4.0 – 10.0	6.0 – 13.0	0.003*	0.027*	0.857	0.006*
Mean ± SD	8.35 ± 1.39	7.10 ± 1.48	8.60 ± 1.39				
Similarities							
Min.-Max.	6.0 – 11.0	4.0 – 10.0	7.0 – 12.0	<0.001*	0.004*	0.561	<0.001*
Mean ± SD	8.55 ± 1.32	7.10 ± 1.41	9.0 ± 1.21				
Comprehension							
Min.-Max.	8.0 – 12.0	5.0 – 11.0	8.0 – 13.0	<0.001*	<0.001*	0.938	<0.001*
Mean ± SD	9.85 ± 1.14	7.85 ± 1.57	9.70 ± 1.22				
Performance IQ							
Min.-Max.	83.0 – 99.0	68.0 – 99.0	85.0 – 103.0	<0.001*	0.002*	0.641	<0.001*
Mean ± SD	92.55 ± 4.94	84.85 ± 8.82	94.50 ± 5.02				
Object assembly							
Min.-Max.	8.0 – 14.0	8.0 – 12.0	8.0 – 13.0	0.488	0.550	0.993	0.623
Mean ± SD	9.80 ± 1.47	9.35 ± 1.14	9.75 ± 1.25				
Picture completion							
Min.-Max.	6.0 – 12.0	3.0 – 9.0	6.0 – 13.0	<0.001*	<0.001*	0.908	0.001*
Mean ± SD	8.15 ± 1.27	6.05 ± 1.61	7.95 ± 1.43				
Mazes							
Min.-Max.	6.0 – 14.0	4.0 – 11.0	8.0 – 15.0	<0.001*	0.001*	0.335	<0.001*
Mean ± SD	9.0 ± 1.78	6.85 ± 1.81	9.80 ± 1.47				
Geometric design							
Min.-Max.	7.0 – 14.0	4.0 – 13.0	8.0 – 14.0	0.005*	0.009*	0.867	0.034*
Mean ± SD	9.70 ± 1.81	7.90 ± 2.13	9.40 ± 1.27				
Block design							
Min.-Max.	4.0 – 12.0	3.0 – 10.0	6.0 – 12.0	<0.001*	0.001*	0.954	<0.001*
Mean ± SD	7.95 ± 1.70	6.0 ± 1.72	8.10 ± 1.17				

p_1: p value for comparing between group A with group B and group A
p_1: p value for F test (ANOVA) for comparing between the different studied groups
p_2: p value for Post Hoc test (Scheffe) for comparing between group A and B
p_3: p value for Post Hoc test (Scheffe) for comparing between group A and C
p_4: p value for Post Hoc test (Scheffe) for comparing between B and C
***:** Statistically significant at $p \leq 0.05$

showed significantly reduced cognitive performances compared to patients before chemotherapy. This may be explained by deleterious effects of corticosteroids especially dexamethasone which is used intensively during the first 6 months of treatment on verbal performance by affecting short term memory in the setting of high drug concentration in hippocampus [14]. Wilson et al [15] demonstrated white matter changes in patients with ALL who were treated with chemotherapy that consisted of prednisone, vincristine, L-asparaginase and methotrexate.

Although different mechanisms have been postulated to explain the underlying neurological basis of neurocognitive dysfunction;

Table 4 Role of gender in intelligence quotient (IQ) in group A and group B.

	Group A			Group B		
	Sex		p	Sex		p
	Male (n = 13)	Female (n = 7)		Male (n = 8)	Female (n = 12)	
Full scale IQ						
Min.-Max.	87.0 – 99.0	88.0 – 101.0	0.854	75.0 – 99.0	72.0 – 97.0	0.111
Mean ± SD	95.31 ± 4.57	95.71 ± 4.82		91.38 ± 7.52	85.50 ± 7.76	
Verbal IQ						
Min.-Max.	94.0 – 106.0	96.0 – 109.0	0.250	82.0 – 103.0	80.0 – 99.0	0.118
Mean ± SD	98.38 ± 3.66	100.57 ± 4.39		95.88 ± 6.47	91.0 ± 6.54	
Information						
Min.-Max.	9.0 – 13.0	10.0 – 15.0	0.660	9.0 – 16.0	8.0 – 13.0	0.030*
Mean ± SD	11.0 ± 1.15	11.29 ± 1.70		12.38 ± 2.13	10.50 ± 1.45	
Vocabulary						
Min.-Max.	9.0 – 16.0	10.0 – 12.0	0.354	10.0 – 13.0	9.0 – 13.0	0.560
Mean ± SD	11.62 ± 1.98	10.86 ± 0.90		11.38 ± 1.06	11.08 ± 1.08	
Arithmetic						
Min.-Max.	6.0 – 12.0	7.0 – 11.0	0.403	6.0 – 10.0	4.0 – 9.0	0.513
Mean ± SD	8.15 ± 1.41	8.71 ± 1.38		7.38 ± 1.30	6.92 ± 1.62	
Similarities						
Min.-Max.	6.0 – 11.0	7.0 – 11.0	0.459	4.0 – 10.0	5.0 – 9.0	0.709
Mean ± SD	8.38 ± 1.39	8.86 ± 1.21		7.25 ± 1.83	7.0 ± 1.13	
Comprehension						
Min.-Max.	8.0 – 11.0	9.0 – 12.0	0.095	6.0 – 11.0	5.0 – 10.0	0.230
Mean ± SD	9.54 ± 0.97	10.43 ± 1.27		8.38 ± 1.60	7.50 ± 1.51	
Performance IQ						
Min.-Max.	83.0 – 99.0	85.0 – 97.0	0.657	72.0 – 96.0	68.0 – 99.0	0.284
Mean ± SD	92.92 ± 5.22	91.86 ± 4.67		87.50 ± 7.48	83.08 ± 9.49	
Object assembly						
Min.-Max.	8.0 – 14.0	8.0 – 12.0	0.903	8.0 – 12.0	8.0 – 11.0	0.391
Mean ± SD	9.77 ± 1.59	9.86 ± 1.35		9.63 ± 1.19	9.17 ± 1.11	
Picture completion						
Min.-Max.	7.0 – 12.0	6.0 – 10.0	0.463	4.0 – 9.0	3.0 – 7.0	0.113
Mean ± SD	8.31 ± 1.32	7.86 ± 1.21		6.75 ± 1.83	5.58 ± 1.31	
Mazes						
Min.-Max.	6.0 – 11.0	7.0 – 14.0	0.304	5.0 – 8.0	4.0 – 11.0	0.432
Mean ± SD	8.69 ± 1.44	9.57 ± 2.30		6.50 ± 0.93	7.08 ± 2.23	
Geometric design						
Min.-Max.	8.0 – 14.0	7.0 – 11.0	0.037*	5.0 – 13.0	4.0 – 11.0	0.429
Mean ± SD	10.31 ± 1.70	8.57 ± 1.51		8.38 ± 2.20	7.58 ± 2.11	
Block design						
Min.-Max.	4.0 – 10.0	6.0 – 12.0	0.532	4.0 – 10.0	3.0 – 7.0	0.060
Mean ± SD	7.77 ± 1.54	8.29 ± 2.06		6.88 ± 1.96	5.42 ± 1.31	

p: p value for Student t-test for comparing between the two studied group

*: Statistically significant at $p \leq 0.05$

damage to cortical and subcortical white matter has received the most attention [16]. Iuvone et al [17] reported that children with ALL who had been treated with a combination of cranial radiation therapy and intrathecal methotrexate evidenced brain calcification on neuroimaging scans. The number of doses of intrathecal methotrexate was associated with these calcifications and with neurocognitive decline. Although cranial radiotherapy (CRT) has been strongly implicated in white matter changes, chemotherapy alone may have similar effects [18].

Also, methotrexate used either orally or intrathecally may induce white matter damage due to direct neuronal toxicity, ischemic white matter changes and impaired methylation resulting in impaired neurocognitive function [19,20].Moreover, methotrexate used intravenously in high doses, interferes with the metabolism of folic acid which is necessary for normal development and the optimal functioning of neurons in the central nervous system [21].This neurotoxicity is even more

Table 5 Comparison of the intelligence quotient (I.Q) between children with ALL who received combined therapy (cranial irradiation and chemotherapy) (group B_1) and children with ALL who did not receive cranial irradiation (group B_2).

	group B_1 (n = 14)	group B_2 (n = 6)	p
Full scale IQ			
Min.-Max.	72.0 - 94.0	95.0 - 99.0	<0.001*
Mean ± SD	84.14 ± 6.64	96.50 ± 1.38	
Verbal IQ			
Min.-Max.	80.0 - 97.0	96.0 - 103.0	<0.001*
Mean ± SD	90.21 ± 6.17	99.33 ± 2.58	
Information			
Min.-Max.	8.0 - 13.0	12.0 - 16.0	0.001*
Mean ± SD	10.43 ± 1.45	13.17 ± 1.60	
Vocabulary			
Min.-Max.	9.0 - 12.0	10.0 - 13.0	0.204
Mean ± SD	11.0 ± 0.96	11.67 ± 1.21	
Arithmetic			
Min.-Max.	4.0 - 10.0	6.0 - 9.0	0.445
Mean ± SD	6.93 ± 1.64	7.50 ± 1.05	
Similarities			
Min.-Max.	4.0 - 9.0	7.0 - 10.0	0.022*
Mean ± SD	6.64 ± 1.28	8.17 ± 1.17	
Comprehension			
Min.-Max.	5.0 - 9.0	7.0 - 11.0	0.027*
Mean ± SD	7.36 ± 1.28	9.0 ± 1.67	
Performance IQ			
Min.-Max.	68.0 - 92.0	89.0 - 99.0	0.002*
Mean ± SD	81.14 ± 7.67	93.50 ± 3.73	
Object assembly			
Min.-Max.	8.0 - 11.0	8.0 - 12.0	0.095
Mean ± SD	9.07 ± 0.92	10.0 ± 1.41	
Picture completion			
Min.-Max.	3.0 - 7.0	6.0 - 9.0	0.001*
Mean ± SD	5.36 ± 1.22	7.67 ± 1.21	
Mazes			
Min.-Max.	4.0 - 9.0	6.0 - 11.0	0.029*
Mean ± SD	6.29 ± 1.49	8.17 ± 1.94	
Geometric design			
Min.-Max.	4.0 - 13.0	8.0 - 11.0	0.303
Mean ± SD	7.57 ± 2.38	8.67 ± 1.21	
Block design			
Min.-Max.	3.0 - 7.0	6.0 - 10.0	<0.001*
Mean ± SD	5.21 ± 1.12	7.83 ± 1.47	

p: p value for Student t-test for comparing between B_1 and B_2 Cranial radiation

severe in combination with CRT, probably due to the interruption of the blood-brain barrier by radiation [22]. Reddick WE et al reported that increasing exposure, which corresponding to more courses and higher doses of IV MTX, influenced the prevalence of leukoencephalopathy in children with ALL treated with high doses of MTX [23]. Furthermore, Bhojwani et al concluded that MTX-related clinical neurotoxicity is transient, and most patients can receive subsequent MTX without recurrence of acute or subacute symptoms [24].

Other suggested mechanisms of treatment induced neurocognitive problems include: exogenous glucocorticoids that have negative effects on cognitive function as recently documented by Waber et al [14] who put a hypothesis that dexamethasone therapy can increase risk for late cognitive effects in children treated for ALL. The center mostly affected is the hippocampus [25-27], where neurons are affected by prolonged exposure to high circulating levels of corticosteroids that induces neuropathological alterations, such as dendritic atrophy of hippocampal or cortical neurons [28,29]. In experimental and clinical studies conducted by using dexamethasone (DEX), it has been reported that DEX adversely affects learning and memory skills [30]. Glucocorticoids

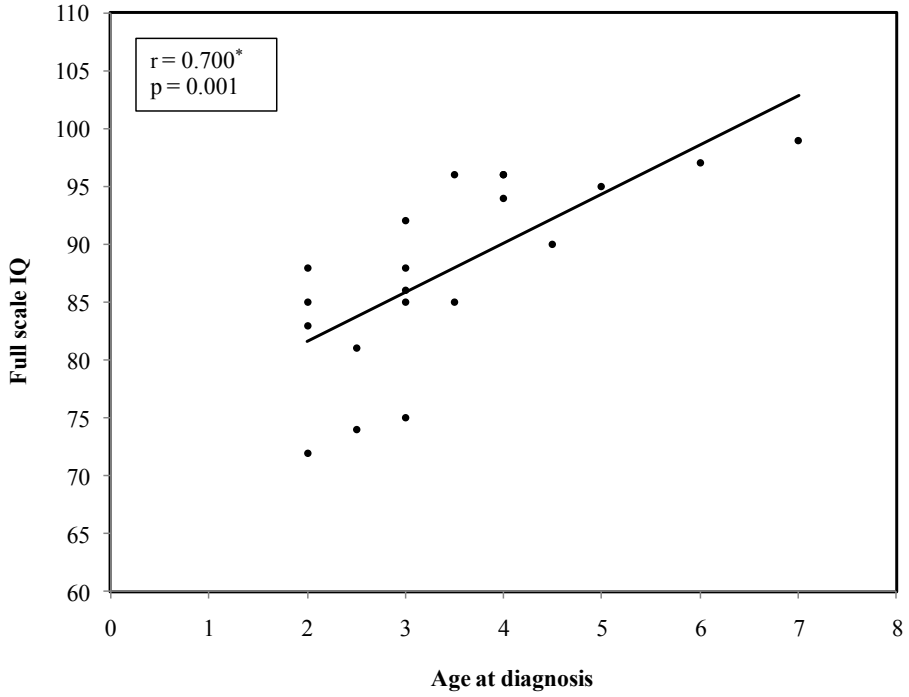

Figure 1 Correlation between the age of diagnosis (in years) and FSIQ in children who completed 3 years of treatment (group B).

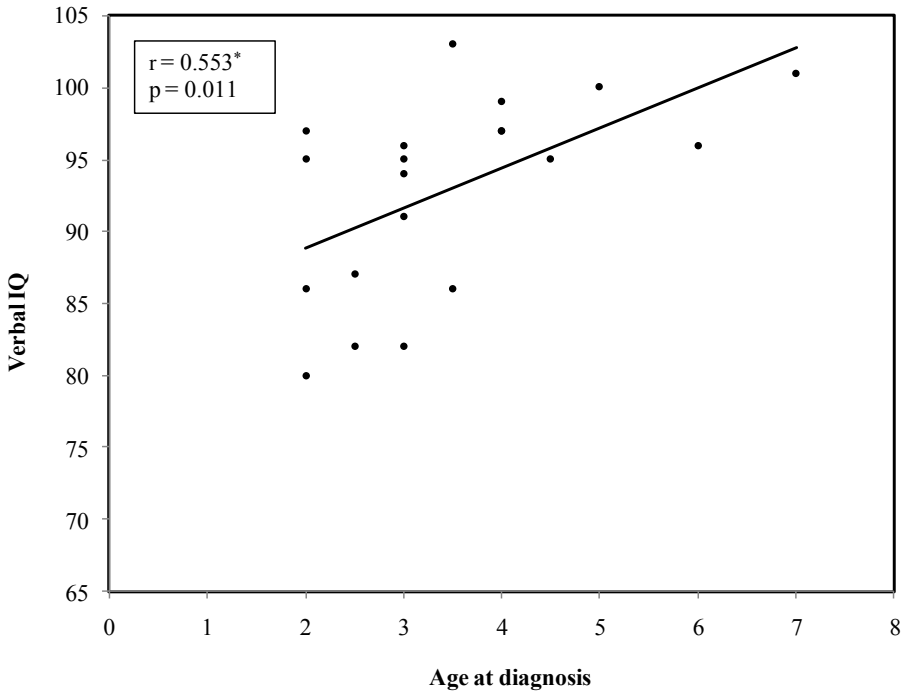

Figure 2 Correlation between the age of diagnosis (in years) and verbal IQ in children who completed 3 years of treatment (group B).

lead to excessive stimulation of postsynaptic receptors and excitoxic neuronal death by apoptosis [31].

Other mechanism is nucleoside analogues, including cytosine arabinoside, which are used intrathecally or intravenously have been reported to cause irreversible neurotoxicity and leukoencephalopathy that can develop weeks to months after exposure [32].

In the present study, there was no statistically significant sex-

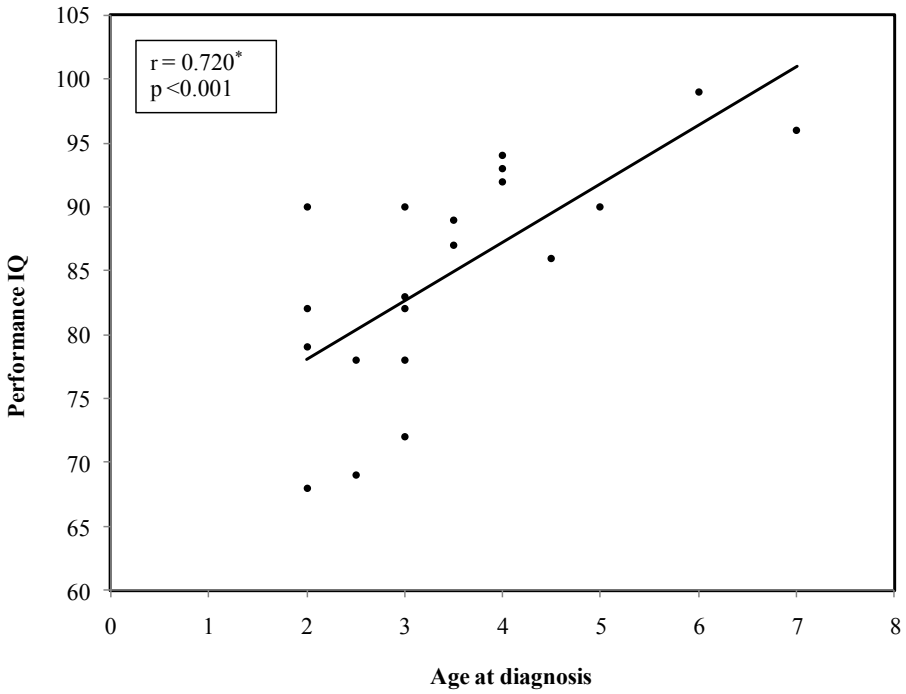

Figure 3 Correlation between the age of diagnosis (in years) and performance IQ in children who completed 3 years of treatment (group B).

related difference of cognitive function in ALL survivors. In agreement with our result, Kingma and colleagues [33] reported that no difference between girls and boys could be recognized. Furthermore, Conklin HM et al reported neither age at diagnosis nor sex was associated with risk for below-average cognitive performance [34].

In the present study, there was no statistically significant difference between the different social classes in ALL survivors who completed treatment and in children receiving chemotherapy for ALL.

The present study demonstrated that there was a positive correlation between cognitive function (FSIQ, Verbal IQ and Performance IQ) and age at diagnosis in ALL survivors after completion of 3 years of treatment. Age at diagnosis (and hence at CNS prophylaxis) is a significant factor in the degree of cognitive deficit experienced by patients, with a larger effect occurring with younger age. Numerous neurocognitive outcome studies have found that a younger age at diagnosis increases the risk of disabilities [35]. Supporting to our result, Iuvone et al, Anderson et al, Langer et al, Jannoun et al and Riccardi et al, showed a greater neurotoxic effect of chemotherapy or cranial radiation or both when given to the youngest patient [17,36,37].

It has been suggested that age at treatment is variable for underlying neurodevelopmental maturity [16]. while development of cortical gray matter peaks at approximately the age of 4 years, cortical white matter volume continues to rise until about age of 20 years [38]. Therefore, those who are younger at treatment generally have less fully developed white matter. However, since both younger and older patients have been shown to lose white matter at similar rates [39], the younger irradiated patients continue to display reduced total white matter volume following radiation treatment. These deficits in white matter volume among younger patients have also been associated with increased intellectual morbidity [16,39].

Von der Weid et al [40] found that former known risk factors described in children treated with prophylactic CNS irradiation, like a younger age at diagnosis of ALL remained valid in chemotherapy-only treated patients. The abandonment of prophylactic CNS irradiation and its replacement by a more intensive systemic and intrathecal chemotherapy led to a reduction, but not the disappearance of late neuropsychological sequelae.

Conclusion

Cognitive function (IQ) is not affected by the occurrence of ALL itself but it may show a progressive decline with ALL treatment.

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