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Neurocognitive Function of Children suffering from Acute Lymphoblastic Leukemia in Southern Iran

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Abstract

Background: Children with acute lymphoblastic leukemia (ALL) are prone to neurotoxicity and consequently neurocognitive function impairment mainly due to undergoing different treatment modalities. In the current investigation, neurocognitive function of children with ALL was compared to that of healthy children.

Materials and Methods: In this cross-sectional study, 155 ALL and 155 age- matched healthy children in Shiraz, Southern Iran, were included and evaluated using Continuous Performance Test (CPT).

Results: Mean age of the patients was 9.9± 2.4 years. The number of wrong responses and duration of response did not lead to significant difference between healthy and affected children. In the age group less than 12 years old, the frequency of no-response was higher in the case group compared to control group both in boys and girls (P = 0.012, P = 0.006 respectively). In addition, in male patients younger than 12 years old, the number of correct responses was significantly less than that of controls (P = 0.010). Patients underwent concurrent radiotherapy and chemotherapy needed significantly more time for responding compared to patients in whom chemotherapy were discontinued and were in remission (P=0.001).

Conclusion: Based on the results, ALL children younger than 12 years old showed some defects in cognitive function. Moreover, it was more prominent in young boys compared to young girls. Regardless of the type of treatment regimens, early detection of neurocognitive disorders should be warranted in this high-risk population with more focus on boys and younger children. Psychological support and appropriate interventions can help improve cognitive function, reduce the disruption of education, and enhance the social and family relationships.

Keywords: Children, Leukemia, Neurocognitive, Psychology

Introduction

The prevalence of childhood cancer is rare, accounting for 1 to -2 per 10000 populations. Recent advances in early detection and treatment have resulted in increased survival rate, particularly in leukemia sufferers (1).

Acute lymphoblastic leukemia (ALL) is the most common malignancy of childhood, making up 25% of all cancers and 75% of cases with leukemia (2). Due to the advancement in management, nowadays, the 5 years' survival rate of children with ALL has been increased and estimated to be approximately 85%. The treatment consists of multi- drug chemotherapy with different intensity based on risk group, the recurrence risk, and prediction of long-term complications. In some high-risk cases, the cranial radiotherapy (CRT) is recommended (3, 4). Some documentary evidence indicates the long-term neurocognitive dysfunction due to CRT neurotoxicity in children, especially young girls (5, 6). However, chemotherapy that is administered directly into the central nervous system as intrathecal methotrexate injection is gradually replacing CRT (2).

Conventional treatment for ALL is usually 24-30 months. All protocols include CNS prophylaxis treatment to prevent relapses.

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Current chemotherapy protocols include different groups of drugs such as glucocorticoids, antifolates, and nucleoside analogs. All these drugs can lead to neurotoxicity(3). Numerous articles have addressed the effects of radiation on neurocognitive dysfunction but the effects of chemotherapy have been less studied. In two studies conducted by Kingma and Anderson et al, the prevalence of neurocognitive dysfunction in ALL patients after CRT treatment and chemotherapy was investigated. They reported the worse neurocognitive dysfunction after radiotherapy (5, 6).

Moleski et al. reviewed the neuropsychological, neuroanatomical, and neurophysiological consequences of central nervous system (CNS) chemotherapy in ALL children. He concluded that although adverse cognitive sequelae of CNS prophylaxis are not preventable in these patients, alternative learning strategies should be used to manage the experienced neurological deficits in ALL survivors.(7).

In another study by Elisabeth Lofstad et al, cognition was assessed by Wechsler Intelligence Test Scale for Children-Third Edition (WISC-III). They concluded that chemotherapy in patients can lead to reduced brain growth resulting in development of some cognitional complications, although the test results maybe within the normal range (8).

Determination of cognitive impairment in children following chemotherapy can be helpful for public health providers and educational systems. Reduced Intelligence Quotient (IQ) is considered as an important risk factor in psychosocial disorders, mental diseases, and problems at school and some interventions may be helpful in the prevention of drop in IQ. Due to disagreement about the effect of different methods of treatment (chemotherapy or concurrent chemotherapy and radiation therapy) and the small number of studies in this regard on children, this study was designed to compare children with leukemia with healthy children in terms of neurocognitive function and with respect to treatment with chemotherapy or with concurrent chemotherapy and radiotherapy.

Materials and Methods

In this cross-sectional study, the case group consisted of 155 patients with ALL diagnosed between the ages of 6-18 years and received treatment at least 6 months or who were in remission after discontinuing treatment. Considering values of P (30%), α (0.05), and (d) (7.5%) and according to Kevin R et al., (9), a sample size of 155 persons in each group was calculated using Medcalc software. The case group was selected using convenience sampling method from patients who were eligible for the study. All patients referred to Amir Oncology Hospital, a tertiary referral center in Shiraz, Southern Iran. The control group included 155 healthy children, who were matched in age with the case group, referred to the pediatric clinic for check-up. The Strengths and Difficulties Questionnaire (SDQ) was used to abandon the underlying perceptual and cognitive problems in the control group. The inclusion criteria included aging between 6-18 years and passing at least 6 months of chemotherapy. Patients could be under treatment or in remission after discontinuation of treatment.. Patients with history of bone marrow transplantation, neurodevelopmental syndromes, or other CNS diseases, and patients with congenital hypothyroidism were excluded. Informed written consent was obtained from the patients or their caregivers.

Treatment included chemotherapy or concurrent chemotherapy and radiation therapy.

Remission was induced using three or four drugs (i.e., vincristine, prednisone, asparaginase, with or without an anthracycline depending on the risk classification) as well as intrathecal chemotherapy. short intensive chemotherapy courses (no maintenance

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cycles) was used for the treatment of mature B-cell ALL . To prevent the occurrence of disease in CNS sanctuary sites, all patients received prophylactic CNS therapy (intrathecal chemotherapy) with adjusted doses of Methotrexate, cytozar and hydrocortisone regarding patient's ages. All patients with CNS involvement at diagnosis received CNS radiotherapy in addition to age adjusted intrathecal chemotherapy. In patients with intermediate- and high-risk T cell ALL, patients received prophylactic cranial radiation therapy (1200 cGy) during delayed intensification. All T-ALL patients who are CNS 3(> 5 WBCs/mm3, blasts on cytocentrifuge slide) at diagnosis received 1800 cGy during delayed intensification (10).

Neurocognitive performance of children was evaluated by Continuous Performance Test (CPT) in both control and case groups. This clinical test was performed by an expert psychiatrist for all patients. CPT is one of the most common clinical measures of sustained attention and vigilance (11). This clinical assessment is based on selective attention or vigilance following an infrequently occurring stimulus. These evaluations focus on rapid presentation of continuously changing stimuli with a designated “target” stimulus or “target” pattern with different time period based on the task but it should be enough to measure sustained attention (12).

Ethics Committee approval was obtained by the Research Advisory Council at Shiraz University of Medical Sciences (Ethical approval number=86/1018).

Statistical analysis

Statistical analysis

Statistical analysis was performed by SPSS (version 21, Chicago, Illinois, USA). The normality of quantitative variables was assessed by Kolmogorov-Smirnov test. Descriptive results were reported as mean, standard deviation, median and interquartile range. The quantitative variables were compared between the two groups using Student t-test and Mann-Whitney test. Qualitative variables were analyzed by chi-square test. The quantitative variables were assessed among three groups using Kruskal–Wallis test. P-value less than 0.05 was considered statistically significant.

Results

The average age of patients in the case and control groups was 9.9± 2.4 years and 10.2 ± 3.3 years, respectively, leading to no statistically significant difference between two groups (p=0.699). In terms of gender, 62.9% of cases and 37.1% of control groups were boys, suggesting not statistically significant difference (P <0.001). Therefore, the statistical analysis was conducted in two stratums of boys and girls separately. Table I shows the median and interquartile range scores according to gender in case and control groups.

Only in boys, the rate of non-response in the case group was more than that in the control group; however, the rate of correct responses in the case group was less than that in the control group, revealing a statistically significant difference (P-value = 0.017 versus P-value = 0.031).

In the next step, the patients were divided to subgroups based on age (< 12 years old and 12 ≥ years) and based on gender concurrently (Table II). In this stratification, the significant differences were only limited to the age group of less than 12 years old. In this age group, the rate of no- response in each of the two groups of boys and girls was higher than that in the case group (P-value = 0.012 versus P-value= 0.006). In addition, in the boys of age group < 12 years, the rate of correct responses in the case group was significantly less than that in the control group (P-value = 0.010).

To investigate the relationship between treatment status and pattern of responses in case group, four groups were considered. Patients who received chemotherapy, received concurrent chemotherapy and radiotherapy, and patients who had

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underwent one of these regimens and at the time study they were in remission. Only patients underwent concurrent radiotherapy and chemotherapy needed significantly more time for responding compared to patients in whom chemotherapy were discontinued and were in remission (P=0.001) (Table 3).

Table I: Comparison of scores between the case and control groups based on gender

	Case (n=155)		**Control (n=155)**		**P-value**
	Median, interquartile range	**Min-Max**	**Median, interquartile range**	**Min-Max**	
Wrong response					
Male N=151	3,6	0-50	3,4	0-17	0.324
Female N=159	2,4	0-27	2,3	0-28	0.756
No response					
Male N=151	2,5	0-30	1,3	0-30	0.017*
Female N=159	1,4	0-17	1,3	0-10	0.068
Correct response					
Male N=151	144,13	0-150	146, 8.7	119-150	0.031*
Female N=159	146, 7.75	119-150	147,4	121-150	0. 362
Time for responding					
Male N=151	567, 126	0-814	548,149	0-749	0.334
Female N=159	601, 158	409-910	598, 116	439-725	0.376

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Table II: Comparison of scores between the case and control groups based on age group and gender

	Control (n=155)	**Case (n=155)**	**P-value**
	Median, interquartile range	**Median, interquartile range**	
Wrong response			
<12 years			
Males n=100	4(4)	4(6.5)	**0.212**
Females n=126	3(3)	2(5)	**0.623**
≥12 years			
Males n=51	2(2.5)	2(2.25)	**0.584**
Females n=33	1(1.7)	1(1.5)	**0.910**
No response			
<12 years			
Males n=100	1(3)	2(6)	**0.012***
Females n=126	1(3)	4(7.5)	**0.006***
≥12 years			
Males n=51	0(1.5)	0(1.2)	**0.686**
Females n=33	0(1.7)	0(1)	**0.901**
Correct response			
<12 years			
Males n=100	145(9)	142(16)	**0.010***
Females n=126	146(4)	144(10)	**0.050**
≥12 years			
Males n=51	148(4)	148(3.2)	**0.846**
Females n=33	148(2)	148(2)	**0.873**
Time for responding			
<12 years			
Males n=100	602(123)	603(137)	**0.631**
Females n=126	608(99)	627(126)	**0.089**
≥12 years			
Males n=51	496(91)	512(68)	**0.320**
Females n=33	502(58)	505(66)	**0.606**

*Statistically significant

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Table III: Comparison of scores in different treatment methods

Treatment methods		Median, interquartile range	Min-Max	P- value
Wrong response				
Chemotherapy	A0 N=45	4,8	0-50	
	A1 N=73	2,3.5	0-41	0.073
Chemotherapy and Radiotherapy	B0 N=24	3,4.5	0-28	
	B1 N=13	4,5.5	0-25	
No response				
Chemotherapy	A0 N=45	2,9.5	0-30	0.068
	A1 N=73	1,4	0-30	
Chemotherapy and Radiotherapy	B0 N=24	4,5.7	0-17	
	B1 N=13	2,3	0-9	
Correct response				
Chemotherapy	A0 N=45	144,19	90-150	
	A1 N=73	146, 7	0-150	
Chemotherapy and Radiotherapy	B0 N=24	142.5,7.5	116-150	0.115
	B1 N=13	143, 8	120-150	
Time for responding				
Chemotherapy	A0 N=45	564,174	0-910	
	A1 N=73	549, 129	0-759	
Chemotherapy and Radiotherapy	B0 N=24	647, 130	463-800	0.016*
	B1 N=13	611, 132	463-765	

A0: Patients Under chemotherapy; A1: Remission and discontinuing treatment; B0: Patients Under chemo-radiotherapy; B1: Remission and discontinuing chemo-radiotherapy.

Discussion

In this study, the cognitive function of 155 children with leukemia was compared with that of healthy children using CPT. In boys less than 12 years old, the rate of non-response in the patient group was more, but the rate of correct responses in these patients was less than that in healthy children. The status of girls seems better, as the girls less than 12 years old only showed a significant high rate of non-response compared to healthy children. Different methods of treatment, including chemotherapy and radiation therapy and the patient's condition in terms of remission, led to no significant difference

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in two groups. regarding rate of non-response, wrong responses, and correct responses However, patients underwent concurrent radiotherapy and chemotherapy needed significantly more time for responding compared to patients in whom chemotherapy were discontinued and were in remission. Various mechanisms are involved after treatment of cancer in children with neurocognitive dysfunction, but cortical and sub-cortical white matter injury may be the main mechanism for the development of these dysfunctions (9, 13, 14). In many patients, white matter abnormalities are transient and a reduction in the prevalence, incidence, and intensity with the passage of time following treatment was observed (15-17).

In some studies, radiographic leukoencephalopathy was reported in up to 80% of the children who underwent radiotherapy treatment. Higher doses and longer courses of intravenous methotrexate therapy were associated with an increased risk of leukoencephalopathy (9, 18, 19).

In pediatric patients with ALL, the CNS chemo- prophylaxis is necessary because the blood-brain barrier effectively prevents exposure of cancer cells to chemotherapeutic agents; therefore, the CNS environment has become a haven for these cells.

Different dosages of systemic MTX are used in various treatment regimens for leukemia in order to influence appropriately the CNS. High-dose of systemic methotrexate with or without radiotherapy, in rare cases, can lead to neurological cognitive disorders (20-22).

In Rodgers et al.'s study (23), the ability of attention among survivors of blood cancer, who were treated without cranial irradiation, was assessed. Similar to our results, they showed that the rate of non-response was significantly different, but the rate of wrong response and reaction time did not differ significantly between groups. Finally, they reported that children treated without cranial radiation did not show more abnormalities than other children.

A study by Kaden-Lottick et al., (2009) was conducted to compare neurological function in children with ALL who had been treated with intrathecal chemotherapy. They concluded that the absence of a reply, the rate of incorrect response, and reaction time did not differ significantly between the methotrexate alone and triple methotrexate- cytozar-hydrocortisone groups, but they differed significantly between case group and the control group (15).

Several studies revealed the correlation of leukoencephalopathy of small volume of white matter with cognitive impairment. Although these disorders among patients received radiation were mild (generally fall in IQ of about 10), those who received higher doses at a younger age had a significant higher rate of learning difficulties (9, 23-25).

Based on the results of present study and some other studies, the neurocognitive dysfunction was more prevalent in younger age groups, reflecting the greater impact of treatment on the neurocognitive function at younger ages (26, 27). In another study by Krull et al, it was observed that children, especially girls treated at a younger age, were more susceptible to radiation to skulls (18).

In a meta-analysis by Peterson et al (26) in 2008, the - neuropsychological and academic function in children with ALL who were treated with chemotherapy was reviewed. ALL survivors showed impairment in multiple domains including intelligence and academic achievement, processing speed, verbal memory, and some aspects of executive function and motor skills. However, visual motor skills and visual memory was not impaired ALL survivors. Reduction in neuropsychological functions like processing speed, attention, and short-term memory in children treated with radiation therapy was reported in some other studies (9, 24, 26).

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It seems that the decline in intellectual performance and the cognitive dysfunction have been progressive and associated with increasing duration of radiation therapy (18). In the present study, the impact of different treatment methods on neurocognitive function was evaluated. The only significant finding was prolonged duration for responding in patients who underwent both radiotherapy and chemotherapy compared to patients in whom chemotherapy was discontinued and they were in remission. Rate of non-response, wrong responses, and correct responses were similar among different treatment groups. Similarly, few studies showed no significant difference between the two groups of treatment (21, 27). However, two other studies reported worse neurocognitive dysfunction in ALL patients who received concurrent chemotherapy and radiotherapy (5, 6).

Lofstad et al., stated that although the results of neurocognitive assessment of children treated as ALL were in the normal range, chemotherapy in patients led to reduced brain development and thus the known side effects (8).

Compared with cranial radiation therapy, treatment with chemotherapy causes neurological disorders, including cognitive processes, attention, information processing speed, memory, verbal comprehension, visual-spatial skills, and visual-motor function and performance, but in summation the overall thought performance is maintained better (16, 21, 27, 28).

In general, it seems that long-term survivors of ALL have modest achievement in reading and writing abilities, but they have a more significant decline in math performance (17, 21, 28).

According to the results of our study, cognitive performance among boys less than 12 years old was significantly different between case and control groups. This result is consistent with findings of other studies, in which age and female gender were reported as risk factors for poor outcome of cognitive neurological function after chemotherapy (14, 22).

One of the limitations of this study was the difference of gender ratio between patients and healthy children. This limitation was solved by stratification method and doing separate analysis in boys and girls. Nonetheless, the large sample size of patients was the strength point of our study.

Conclusion

Based on the results, ALL children younger than 12 years, especially male gender are more prone to neurocognitive dysfunction regardless of the type of treatment methods. Early detection of neurocognitive disorders should be warranted in this high-risk population with more focus on boys and younger children. Psychological support and appropriate interventions can help improve cognitive function, reduce the disruption of education, and enhance the social and family relationships.

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Authorship contribution

Soheila Zareifar drafted the manuscript and designed the study. Ali Alavi Shoshtari designed the study, too. Aida Abrari participated in data collection and drafted the manuscript. Sezaneh Haghpanah designed the study, drafted the manuscript, and performed statistical analysis. All authors read and approved the final manuscript. This manuscript was based on the thesis by Dr Aida Abrari for her medical degree (Ethical approval number=86/1018).

Conflict of interest

The authors declare no conflict of interest.

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