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.
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 cognitive 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...
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, cytozor 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 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 strata of boys and girls separately. Table I shows the median and interquartile range scores according to gender in case and control groups.

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 non-response in each of the two groups of boys and girls was higher than that in the control 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...
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**

<table>
<thead>
<tr>
<th></th>
<th>Case (n=155)</th>
<th>Control (n=155)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Wrong response</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3.6</td>
<td>0-50</td>
<td>0.324</td>
</tr>
<tr>
<td>N=151</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2.4</td>
<td>0-27</td>
<td>0.756</td>
</tr>
<tr>
<td>N=159</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>No response</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2.5</td>
<td>0-30</td>
<td>0.017*</td>
</tr>
<tr>
<td>N=151</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.4</td>
<td>0-17</td>
<td>0.068</td>
</tr>
<tr>
<td>N=159</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Correct response</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>144,13</td>
<td>0-150</td>
<td>0.031*</td>
</tr>
<tr>
<td>N=151</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>146,7.75</td>
<td>119-150</td>
<td>0.362</td>
</tr>
<tr>
<td>N=159</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Time for responding</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>567,126</td>
<td>0-814</td>
<td>0.334</td>
</tr>
<tr>
<td>N=151</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>601,158</td>
<td>409-910</td>
<td>0.376</td>
</tr>
<tr>
<td>N=159</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>
Table II: Comparison of scores between the case and control groups based on age group and gender

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

*Statistically significant
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.

Table III: Comparison of scores in different treatment methods

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

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

Acknowledgement
Our sincere thanks go to Sheryl Nikpour for improving English writing of this manuscript.

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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