EXECUTIVE CONTROL ABILITIES AND SELF-REGULATION IN SURVIVORS OF CHILDHOOD ACUTE LYMPHOCYTIC LEUKEMIA

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ABSTARCT

OBJECTIVE: The objective of the study was to examine executive control and self-regulation abilities in survivors of childhood Acute Lymphocytic Leukemia (ALL).

METHODS: Thirty-five survivors of childhood ALL from Sahukat Khanum Memorial Cancer Hospital, Children Hospital and Jinnah Hospital participated in the study. Thirty-five demographically matched healthy children were recruited from local community. Participants completed Trail Making Test and Self-regulation Questionnaire.

RESULTS: Results showed that there were significant differences between ALL and control group on TMT-part A and TMT-part B. In contrast to control group, ALL group showed executive control deficit. In addition, both groups performed significantly different on self-regulation questionnaire. ALL group in contrast to control group showed impaired emotional, behavioral and cognitive regulation.

CONCLUSION: Survivors of childhood ALL have marked deficits in social cognition. Treatment protocols might also focus on psychosocial deterioration for better patient care.

KEY WORDS Executive Function, Emotion, Self-Regulation, Acute Lymphocytic Leukemia, Pediatric Cancer.

INTRODUCTION

Cancer is emerging as a major cause of mortality all around world. Pediatric cancer is challenging experience for the child as well as family[1]. Leukemia is the type of cancer affecting bone marrow and blood. Acute lymphocytic leukemia (ALL) is common type of leukemia and is a result of malignant production of lymphoid precursor cells in bone marrow and blood. Symptoms of ALL include breathing problems, infections, laziness, fever and blood loss. It is estimated that Pakistani children with ALL have higher burdens of Leukemia which might result in poor prognosis[2] . Though treatment protocols for ALL has been advanced over the years which increased survival rate, yet deficits in several areas of cognition, emotion and behavior have been demonstrated by ALL survivors. Treatment protocols destroy leukemic cells present in bone marrow, cerebrospinal fluid and organs. Moreover, treatment inhibits disease metastasis in the central nervous system[3]. Survivors of ALL treated with chemotherapy only showed cognitive deficits in verbal functions, attention, and visual-spatial problem solving[4]. Neurocognitive impairment was also marked in ALL survivors treated without cranial radiation[5]. Behavioral and emotional problems have also been observed in childhood malignancies specifically ALL[6,7]. It has been suggested that cognitive impairment is associated with difficulties in emotion regulation and deficient coping skills in survivors of ALL[8]. Mechanism of neurocognitive deficits are associated with chemotherapy agents which are neurotoxic in nature. Drugs administered intravenously or given orally have adverse effects on cognitive, emotional and behavioral functioning, for instance Methotrexate is associated with changes in white matter of the brain and neurocognitive performance, paralysis and seizures of acute nature[9-12]. Corticosteroids are associated with reduced hippocampal activity and behavioral problems[13]. Vincristine causes peripheral neuropathy[14]. Standard treatment protocol also includes periodic intrathecal methotrexate and corticosteroids directly injected in to the central nervous system. This

therapy has exacerbated neurotoxicity[15]. In addition, there are certain structural brain changes in ALL survivors which are associated with cognitive deficits and difficulties in emotion regulation such as reduced volumes of the prefrontal cortex and cerebral white matter[16,17]. Cerebral hemorrhages are common in ALL survivors cured with cerebral radiation therapy[18]. Intrathecal methotrexate and cranial irradiation are associated with hemosiderin and white matter lesions in ALL survivors[19,20]. It is therefore not clear that neurological complications are due to ALL itself, systematic chemotherapy or cranial radiation.

To date, though studies have examined long-term consequences on cognition, emotion and behavior, but there are no studies in literature which have examined cognitive control and self-regulation abilities in ALL survivors. Therefore, the aim of the present study was to assess executive control and self-regulation abilities of ALL survivors. The current study excluded patients with CNS pathology requiring radiation or surgery because cranial radiation has well documented adverse effects on neuropsychological functioning. The study examined the question whether ALL survivors cured with systematic chemotherapy excluding cranial radiation show any differential performance than healthy subjects. Given the treatment related neurotoxic effects and structural brain changes, it was hypothesized that ALL survivors would be deficient in executive control, emotional, behavioral and cognitive regulation in contrast to healthy control subjects.

METHODS

Thirty-five children and adolescent survivors of childhood ALL and thirty-five demographically matched healthy control children participated in the study (Table I). ALL survivors completed treatment protocol at Jinnah Hospital, Children Hospital and Shaukat Khanum Memorial Cancer Hospital Lahore. Inclusion criterion for ALL survivors were as follows: (i) completed the treatment protocol for standard or high risk childhood ALL (ii) continuous first remission without relapse. Exclusion criterion for ALL group were as

follows: (i) history of CNS pathology, bone marrow transplant, other cancer diagnosis, or major medical illness (ii) neurological or psychiatric disorder. The inclusion criterion for healthy control children were: (i) no history or present diagnosis of cancer (ii) no known neurological or psychiatric illness.

Measures

Trail Making Test (TMT)

TMT [21] is a neuropsychological instrument to examine executive control abilities. The test consists of two parts. In Part A, subjects are required to connect numbered circles whereas part B required subjects to connect a series of numbered-lettered circles alternating between these sequences. TMT part A reflects visuoperceptual abilities and part B indicates working memory and task switching abilities.

Self-Regulation Questionnaire

Self-regulation questionnaire[22] measures emotional, cognitive and behavioral control on three separate subscales. It is a 13-item questionnaire. Each item is to be assessed how true is the statement for the subject on response categories ranging from (1=never true) to (4=always true). Higher scores indicate deficits on emotional and behavioral subscales whereas lower scores on cognitive regulation subscale show impairment. Emotional regulation scale examines the ability to control anger, intense emotional reaction, and regulation of negative emotions. Cognitive regulation measures the ability to control impulse, focus attention to tasks, thinking and planning. Behavioral regulation identifies control over hyperactivity and aggression.

Procedure

The study was approved by the board of studies of The Islamia University of Bahawalpur. All participants and their parents gave written informed consent. The study was conducted in a

single session. Participants completed TMT and self-regulation questionnaire. After completion, they were debriefed and thanked for their participation.

RESULTS

Descriptive statistics were computed for demographic and clinical characteristics (Table I) which showed ALL and control groups were matched on gender, age, and socioeconomic status. TMT scores were recorded as the time (seconds) taken to perform part A and part B by the ALL and control group. Results showed that there was a significant difference between groups on TMT-part A t (34)= 30.82, p<0.001. ALL group were slower to perform TMT-part A (M=35.25, SD=2.38) as compared to control group (M= 16.14, SD= 2.80). There was a significant between group difference on TMT-part B t (34)= 117.98, p<0.001. ALL group (M=105.62, SD=2.38) took more time to complete TMT-part B as compared to control group (M=33.42, SD=2.30). Scores on subscales of self-regulation questionnaire showed significant mean differences between both groups on emotion regulation t (34)= 53.67, p<0.001, behavioral regulation t (34)= 49.61, p<0.001 and cognitive regulation t (34)= 22.22, p<0.001. ALL group (M=18.65, SD=1.10) showed higher scores on emotion regulation as compared with control group (M=5.57, SD=0.85). There was significant higher scores of ALL group (M= 14.97, SD=0.92) on behavioral regulation as compared with control group (M= 4.68, SD=0.75). Moreover, ALL group (M= 3.57, SD=0.85) scored lower on cognitive regulation as compared with control group (M= 10.60, SD=1.55).

DISCUSSION

The present study was conducted to examine executive control and self-regulation in survivors of childhood ALL. There were two important results: (i) survivors of childhood ALL showed deficits in executive control in contrast with healthy control children. Executive control deficits extended over part A and part B of TMT. Part A reflected visual attention and part B showed task switching and set-shifting abilities. (ii) ALL survivors showed deficits on

emotion regulation, behavioral regulation and cognitive regulation contrary with healthy control children. These results are consistent with previous studies which showed neurological complications in survivors of ALL[4] related with neurotoxic effects of treatment. Disease related therapeutic agents such as glucocorticoids and L-asparginase are associated with cerebrovascular events [23]. Methotrexate causes white matter lesions of the brain, seizures and neuropsychological complications [9-12]. Corticosteroids reduce activity of the hippocampus (brain area which is involved in memory and learning) and cause behavioral disorders[13]. Administration of Vincristine cause peripheral neuropathy[14]. Direct injectable agents in to the central nervous system such as intrathecal methotrexate and corticosteroids have neurotoxic effects[15]. Executive control and self-regulation are mainly function of prefrontal cortex of the brain[24]. Deficits in these cognitive areas are consistent with previous findings of reduced volumes in prefrontal cortex and cerebral white matter of the brain[16,17], presence of cerebral hemorrhage, hemosiderin and lesions of the white matter in survivors of childhood ALL[18-20]. Executive control orchestrate memory, thought, action, planning and switching ability which stems from activity of the prefrontal cortex. Deficit in executive control reflect deficient neural signals from the prefrontal cortex to other brain areas to exert control over thinking, action, planning and switching. Signals to the other brain structures whose function is to control emotion and behavior, also gets affected. As a net effect, the active initiation and maintenance of emotional and behavioral regulation gets impaired. In contrast, healthy children showed efficient performance on TMT which reflected intact activity of the neocortical region (i.e., prefrontal cortex). Healthy children demonstrated no deficits in three areas of self-regulation (i.e., cognitive, emotional and behavioral). Results have implications for better management and prevention of cognitive impairment at early stage of the disease. Psychotherapy might be used besides treatment protocol for patient care.

CONFLICT OF INTEREST

Authors declared no conflict of interest.

GRANT SUPPORT AND FINANCIAL DISCLOSURE

NIL

REFERENCES

Table I

Demographic and Clinical Characteristics of ALL and Control Group

	ALL Group (n=35)	**Control Group** (n=35)	
	M (SD)	M (SD)	
Age (range 10-20 years)	14.25 (2.71)	14.34 (2.98)	t (34)=0.33, p=0.73
Gender male/female (male/female %)	17/18 (48.57/51.42%)	17/1817/18 (48.57/51.42%)	
Socioeconomic class			
High (f/%)	11/31.42	11/31.42	
Medium (f/%)	12/34.28	12/34.28	
Low (f/%)	12/34.28	12/34.28	
Age at time of diagnosis (range 1-14 years)	6.97 (3.24)	NA	
Time since treatment completion (range 1-14 years)	7.48 (2.62)	NA	

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