CASE SERIES

Evidence of cognitive flexibility deficits and impaired emotion regulation in childhood survivors of acute lymphoblastic leukaemia: Findings from task switching study

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Abstract

The objective of the current study was to compare cognitive flexibility and emotion regulation between childhood survivors of Acute Lymphoblastic Leukaemia (ALL) and healthy control subjects. Twenty-five childhood survivors of ALL treated with intrathecal chemotherapy between 2013 to 2016 from Shaukat Khanum Memorial Cancer Hospital, Children Hospital and Jinnah Hospital Lahore and twenty-five healthy demographically matched children (control group) participated in the study. Participants performed task switching experiment as a measure of cognitive flexibility and emotion regulation questionnaire for children and adolescents. In contrast to healthy control group, ALL survivors showed impaired cognitive flexibility and emotion regulation. Results have implications for cognitive rehabilitation to improve functions of frontal-cerebellar system in childhood survivors of ALL.

Keywords: Cognition; Acute Lymphoblastic Leukaemia, Emotion, Prefrontal cortex

Introduction

Leukaemia is the most common form of childhood cancer. Acute Lymphoblastic Leukaemia (ALL) is the most prevalent form of leukaemia in childhood. ALL is characterized by accumulation of immature white blood cells in blood and bone marrow. ALL interrupts normal course of cell development by either immature lymphocytes crowding out red blood cells which interfere with normal supply of oxygen to the body or by invading the brain. Advancements in medicine has increased the survival rate of children with ALL but treatment components entail neurotoxic effects (corticosteroids, antifolates, craniospinal irradiation) depleting cognitive resources.[1] Several structural brain abnormalities have been observed in survivors of childhood ALL, for instance reduced volumes in cerebral white matter are associated with deteriorated neurocognitive functioning.[2] Functional magnetic resonance imaging studies have shown that cerebellum and prefrontal cortex are most affected areas of the brain where volumes are reduced. These deficits are concurrent with impaired neuropsychological functioning[3] and emotional disorders in children suffering from ALL.[4] Childhood survivors of ALL have impaired executive functioning which includes inhibition, cognitive flexibility and working memory.[5] Cognitive flexibility is the ability to switch between tasks and is a function of the prefrontal cortex.[6] Higher switch costs indicates deficient cognitive flexibility. Over the past decade, interest has grown in emotion regulation for children's healthy psychological development. There is a supporting evidence that brain pathways emerge from prefrontal cortex which are involved in goal directed behaviour and emotion control.[7] Prefrontal cortex has close connection to emotion centers of the brain, thus influences emotion regulation.[8] Executive functions (e,g, task switching) are also controlled by prefrontal cortex and emotion centers of the brain specifically when decisions to emotions are required. Previous studies have examined cognitive and emotion functioning but relationship between these parameters have never been examined in patient population with ALL. Present study is the first attempt to assess task switching and emotion regulation abilities of patients with ALL. Given that neural pathways monitoring cognition and emotion overlap, it was hypothesized that (i) ALL survivors would show impaired cognitive flexibility (i.e., larger switch costs) and emotion regulation (ii) emotion regulation would be significant predictor of cognitive flexibility.

Case Series

Twenty-five children who were survivors of ALL participated in the study from Shaukat Khanum Memorial Cancer Hospital, Children Hospital and Jinnah Hospital Lahore. Patients received three year protocol of CNS prophylaxis between 2013 and 2016 with treatment components as CNS prophylaxis, induction, consolidation and maintenance. All patients received hydrocortisone, cytosine arabinoside and methotrexate intrathecally for CNS prophylaxis with no irradiation. Inclusion criterion for patients were as follows: age 1-5 years at the diagnosis, no physical or mental disability, no psychiatric disorder, no

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Table-1: Demographic Characteristics of Acute Lymphoblastic Leukaemia (ALL) and Control Group.

	ALL M (SD)	Control M (SD)	
Age in years (range 6-13)	8.56 (1.93)	8.20 (2.19)	t (24)=0.66, p=0.512
Gender male/female (%)	12/13 (48/52)	12/13 (48/52)	
ERQ-CA	28.48 (10.27)	47.80 (3.84)	t (24)=8.75, p=0.000
Socioeconomic status			
	f (%)	**f (%)**	
High	05 (20)	04 (16)	
Middle	15 (60)	16 (64)	
Low	05 (20)	05 (20)	
Task Switching			
	M (SE)	**M (SE)**	
Switch cost	966.15 (84.64)	746.93 (56.85)	t (24)=2.31, p=0.029
Switch	2095.48 (118.69)	1726.60 (118.69)	F(1,48)=4.62,p=0.037
Repeat	1129.32 (120.05)	979.67 (120.05)	

Table-2: Linear Regression for Switch Cost as Dependent variable; Demographic Characteristics and ERQ-CA scores as Independent Variables.

	Standardized β coefficient	t	p
Age	0.149	1.16	0.249
Socioeconomic status	-0.089	-0.568	0.573
Gender	-0.034	-0.253	0.802
ERQ-CA	-0.678	-6.31	0.000

ERQ-CA: Emotion Regulation Questionnaire for Children and Adolescents.

brain damage, injury or focal lesions and no family history of substance abuse. Twenty-five healthy demographically matched children were recruited as control group. The selection criterion for ALL patients were followed for control group except with reference to ALL diagnosis. The study was approved by board of studies of The Islamia University of Bahawalpur and followed protocol according to Helsinki declaration. Then, task Switching Experiment was administered to examine cognitive flexibility. Experiment was designed in E-prime software (version 2.0) with forty-eight faces shown on laptop screen. Participant has to categorize faces according to face expression and face age through manual responses in two forty-one trials. The task gets switched on every second trial throughout the experiment following task switching paradigm[6] ABABAB….First trial of the experiment was no-switch trial. There were 120 trials for each task (60 switch and 60 repeat). Switch costs were measured by subtracting reaction times on switch from repeat trials. The Emotion Regulation Questionnaire for Children and Adolescents-ERQ-CA[9] was administered. ERQ-CA is a 10 -item self-report scale assessing emotion control and regulation in children and adolescents on5 point Likert scale. Higher score indicates higher emotion regulation (range= 10-50). The scale has good reliability (alpha 0.82) and construct validity. Participants of the present study and their parents gave written informed consent. Patient follow up was not involved in the study.

Data was analyzed using Statistical Package for Social Sciences (version 20). Descriptive statistics were used to assess demographic variables. Task switching data was cleaned from outliers by deleting reaction times (RTs) standing above 2.5 standard deviations from each participant's mean. The data for the first trial was removed because of no switch trial. Data for the remaining 240 trials was submitted to repeated measures analysis of variance with factors as Trial 2 (switch versus repeat: within subjects) x Group 2 (ALL versus control: between subjects). Linear regression was conducted to examine predictors of switch costs (dependent variable) with demographic variables (age, gender, socioeconomic status) and emotion regulation as independent variables.

Demographic characteristics are shown in Table-1. Results of task switching data showed significant main effect of Trial F (1, 48)= 282.26, p=0.000, ηp2=0.855. Mean RTs for switch trials were slower as compared to repeat trials (1911 versus 1054 milliseconds). Main effect of Group was not significant F (1, 48)= 2.59, p=0.114, ηp2=0.051, Mean ALL versus control (1612 versus 1353 milliseconds). There was a significant interaction between Trial x Group F (1, 48)= 4.62, p=0.037, ηp2=0.088. ALL group (switch M=2095 milliseconds; repeat M= 1129 milliseconds) Control group (switch M= 1726 milliseconds; repeat M=979 milliseconds). Switch costs (Mean RTs minus Mean RTs on repeat trials) were larger for ALL as compared with control group t (24)= 2.31, p=0.029, 966 versus 746 milliseconds. ALL group showed lesser emotion regulation scores (M=28.48,

SD=10.27) as compared with control group (M=47.80, SD=3.84). Linear regression showed emotion regulation as a significant predictor of switch costs $F(4,49)= 11.96$, $p=0.000$, $R^2=0.51$, $\beta=0.67$, $t=6.31$, $p=0.000$ (Table-2).

Discussion

The main objective of the study was to examine task switching abilities and emotion regulation in survivors of ALL. Results demonstrated that ALL survivors had deficient cognitive flexibility as compared to control group. This result was consistent with previous findings of depleted cognitive resources in ALL survivors due to brain abnormalities such as reduced brain volumes in prefrontal cortex and cerebellum.[1,2] These brain areas are involved in higher order cognitions such as cognitive flexibility. Task switching experiment required modulation of working memory, attention and inhibition whenever the task was switched. Larger switch costs showed that participants were deficient in several functioning areas for an efficient switching. As a result, larger switch costs emerged as compared to healthy control subjects. These deteriorations occur due to structural brain changes observed in ALL survivors such as shrinkage of cerebellar white matter volumes. Children in the present study were in the stage where brain is developing. A normal course of brain development is necessary to conduct higher order cognitive functions. Besides it is noteworthy that during developmental stage, brain is more susceptible to toxic insults such as irradiation and chemotherapy which in turn inhibit normal brain development and cause cognitive deficits. Emotional disorders have been observed in children suffering from ALL after first remission.[4] Neural projections from prefrontal cortex extend to emotion circuits of the brain. Thus, cognition along with emotion functioning is disturbed in survivors of childhood ALL. Results of the present study showed that ALL survivors were deficient in emotion regulation as compared to healthy control subjects. Impaired emotion regulation was also found as significant predictor of deficits in cognitive flexibility.

Conclusion

Deteriorated task switching ability and impaired emotion regulation persist in survivors of ALL after intrathecal methotrexate treatment. Cognitive rehabilitation should be accompanied with treatment protocol to prevent developmental deficits.

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Conflicts of Interests: None.

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