

Behavioral disturbances in children with acute lymphoblastic leukemia

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Abstract: Side effects of chemotherapy, stress and experiencing painful situation probably have been made children with ALL vulnerable to behavioral disorder, but there is no agreement for this, in the literature. The main purpose of the study was investigated how treatment of malignancy and its side effects lead to behavioral disturbance. One hundred and ten (girls=53; boys=57) children with ALL and one hundred and sixteen healthy child (girls=44; boys=72) compare to each other by Disruptive Behavior, Beck Depression Inventory disorder, Children's level of inhibition and anxiety symptoms. Children with ALL displayed difficulties in some aspects of behaviors, especially in behavioral inhibitory. There was no discrepancy between cancer group and control in anxiety and depression. Children with high anxiety and depression reveal more disruptive behavior disorder and behavioral inhibition. The data demonstrated there was very strong relation between duration of hospital stay and behavior disruption in both of sex. This study suggested to health providers to set interventions for decreasing behavioral problems due to treatment of ALL.

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1. Introduction

Acute lymphocytic leukemia (ALL) is the most common form of childhood cancer, accounting for nearly one-third of all diagnoses (Schmiegelow et al., 2008).

Children with cancer often undergo multimodal treatments in which can cause numerous acute and long-term side effects. Painful procedures, hospitalizations, and uncertain prognosis are common stressors that can effect on emotional and behavioral system in these children (Kazak et al., 2006). Furthermore, Children with ALL often suffer from unpredictable and uncontrollable pains that lead to experience anger. The most painful treatments such as injection and, especially, bone marrow transplantation provoke anxiety and avoidance reactions in children with ALL (Kuppenheimer & Brown 2002).

Corticosteroid treatment during ALL maintenance therapy is associated with behavior and emotional disturbances and adversely affects quality of life. Systemic corticosteroids are an essential component of successful leukemia therapy. In fact, children treated with corticosteroids for various medical conditions can display behavioral side effects, including frequent mood swings, increased irritability, depression and anxiety, and problems with behavioral control and aggression during active therapy (Drigan et al., 1992). One of the side effects of chemotherapy as a popular treatment for children with ALL is cortisol suppression (Lam et al., 2009). Cortisol suppression potentially changes strength and stability of emotions and behaviors (Mahachoklertwattana et al., 2004).

Studies point to complex relationships between demographic characteristics of the children with ALL and families. Elevated Behavior Problems scores were associated with younger maternal age at the child's birth, and residence in a single-parent family (Mrakotsky et al., 2011). In addition, side effects of chemotherapy depend on the sex and age. Girls may be more vulnerable than boys, and preschool age children more vulnerable than older children (Maude et al., 2012).

Researchers found out children with cancer would have more social problems than healthy children. They have difficulty maintaining friendships during the treatment process (Kevin et al., 2008). After recovery from illness, survivors are slightly less likely than expected to attend college, and are more likely to be unemployed and not get married as young adults do (Cumberland-Li et al., 2003). ALL survivors had significantly lower composite working memory and cognitive ability in compared to the control group (Kevin, N et al., 2008). Cognitive impairment limits learning and reaction speed. Most of the children with cancer show high level of "repressive adaptive style" in comparing to healthy children. They avoid expressing their negative emotions and suppressing affective problems (Syrjala et al., 2011).

On the other hand, a huge of study results suggest children with cancer reveal that an excellent resilience capacity and well adjustment to cancer and its treatments. Children with ALL receiving chemotherapy were remarkably similar to case controls on measures of emotional well-being and better on

several dimensions of social functioning (Jurbergs et al., 2009). These findings are not supportive of disability/stress models and suggest considerable psychological hardness.

Taken together, several large-scale studies of long-term childhood ALL survivors suggest that some may be susceptible to psychosocial distress and behavioral problems. Some children who are unable to cope effectively with stressful situations are at higher risk for developing emotional and behavioral difficulties (Wadsworth et al., 2004). Executive function impairment may be associated with difficulties in coping and emotion regulation in a subgroup of children treated for ALL.

Most studies had focused on behavior problems in survivors of ALL, but in this study, children who were undergoing treatment were being studied. Therefore, the most important question is how treatment and its side effects cause behavioral disruption in children with ALL.

2. Materials and Methods

2.1. Participants

One hundred and ten (girls=53; boys=57) children with Acute Lymphoblastic Leukemia (ALL) participated in this study. Samplings of cancer groups were selected among patients admitted in a specialized pediatric oncology center (Mahak Hospital). Potential participants were identified from the list of Outpatient Chemotherapy Room and were selected randomly. Eligibility criteria for inclusion in the original study were: 1) the child was between 6 and 12 years old, 2) the child was diagnosed with Acute Lymphoblastic Leukemia (ALL), 3) the child was undergoing chemotherapy. From the initial list of potential participants, two children did not take part in the research. All of the mothers agreed to take part their children in this study. One hundred and sixteen healthy children (girls=44; boys=72), who were almost identical to cancer group in demographic criteria had been recruited from three schools and pre-schools in Tehran. The tests were carried out between 9 to 11 Am. Every day (for the control of time), except holidays. The control group like the children with cancer performed the tests individually.

2.2. Disruptive behavior disorders

The Disruptive Behavior Disorder rating scale (DBD) is a 42-item inventory that assesses all symptoms of externalizing behavior disorders as described in the DSM-IV (Silverman & Hinshaw, 2008). Caregivers, teachers or parents could complete the questionnaire. Higher scores indicate greater severity of problems. Scores above the 95% represented the clinical range. Adequate psychometric properties have been established. Before using DBD in this study, we have revised the test based on mothers interview, and ALL children interview. According to

the results of the interviews, 5 items included the following have added: s/he all the time is nagging, s/he stops playing, s/he stops regular eating, s/he is crying nonstop and s/he is requesting unusual things. Kendall's coefficient of concordance (W) has computed to assess whether there was significant agreement on the rank order among three practitioners, four nurses and four mothers in the pediatric oncology ward.

2.3. Beck Depression Inventory (BDI)

Beck Depression Inventory (BDI) (Beck et al., 1996) was applied to mothers' participates. The BDI is a well established 21-item measure assessing current depressive symptomatology, yielding total scores with a potential range from 0 to 63. A meta-analysis of the BDI's internal consistency estimates yielded a mean coefficient alpha of 0.86 for psychiatric patients and 0.81 for non-psychiatric subjects. The concurrent validity of the BDI with respect to clinical ratings and the Hamilton Psychiatric Rating Scale for Depression (HRSD) were also high. The mean correlations of the BDI samples with clinical ratings and the HRSD were 0.72 and 0.73, respectively, for psychiatric patients. With non-psychiatric subjects, the mean correlations of the BDI with clinical ratings and the HRSD were 0.60 and 0.74, respectively.

2.4. Children's level of inhibition

Children's level of inhibition (Kochanska, 1991) was coded globally on a 4-point scale (1 shows no inhibition; 4 shows much inhibition). The rating was based on all incidents of the following: 1) the lack of approach to paying (e.g., the child does not touch or play with the toys, or walks around the toys); 2) anxious, wary expression or behavior (e.g., the child is timid or fearful); and 3) wary, hesitant response to the stranger (e.g., child retreats from the stranger, freezes, avoids eye contact). The inter-rater reliability was .88 based on 10% of cases coded by two raters. Children who were assessed at different ages were compared; no differences in levels of inhibition were found (Moehler et al., 2006).

2.5. Anxiety symptoms

Symptoms of anxiety in children were assessed by the Child Behavior Checklist (Nakamura et al., 2009). This parent-report measure includes 34 items scored on a three-point scale based on frequency in the past 6 months. The DSM-Oriented Scales for Affective Problems and Anxiety Problems were used to examine the symptoms of anxiety and depression separately. The CBCL has strong reliability and validity, and the agreement between parent and child report of internalizing symptoms on the CBCL and Youth Self Report (YSR) reflect medium to large effects ($r=.39-.48$).

3. Results

General characteristics of the participants are presented in table1. In the cancer group, most of the

subjects were boys, and 72.18% of the participants did not go to school but they can read the text of questionnaires (in most of the cases this was due to their illness and the necessity to continue treatment). On average, they had been challenged with their illness 2.8 years (duration of disease; $M=2.8$ years) and 39.3% of the cancer patients were living in Tehran.

The prediction of the difference between children with cancer and the control group in behavioral disruptions was supported. Table 2 revealed that children with cancer had a significantly worse mean in disruptive behavior disorder ($F=263.82$, $P<0.001$) and behavioral inhibition ($F=197.55$, $P<0.001$), but there was no significant difference between cancer and healthy groups in emotional reactions (depression and anxiety).

A MANOVA was performed with two between subject factors, including gender and behavioral disruptions, one covariant (IQ) and four dependent variables (age, duration of disease, duration

of hospital stay and financial situation). To study how treatment and its side effects impact on the behavioral system in girls and boys with cancer with respect to their age, duration of disease, duration of hospital stay and financial situation. There was a significant interaction of gender \times disruptive behaviors \times depression $F=92.18$ $P<0.001$ $\eta^2=0.041$; gender \times disruptive behaviors \times anxiety $F=113.56$ $P<0.001$ $\eta^2=0.56$; gender \times disruptive behaviors \times hospital stay $F=92.98$ $P<0.001$ $\eta^2=0.12$. Univariate tests revealed the depressed boys showed more inhibition and disruptive behavior (DB: $M=43.21$ $SD=0.3$; CLI: $M=3.8$ $SD=0.24$); anxious girls displayed more disruptive behavior (DB: $M=44.6$ $SD=0.67$; CLI: $M=3.5$ $SD=0.36$); the children had resided more in hospital indicated more disruptive behaviors (DB: $M=42.1$ $SD=0.62$; CLI: $M=2.7$ $SD=0.69$). Duration of disease and financial situation did not show a significant interaction to disruptive behaviors.

Table 1. General characteristic of the study sample

	Children with cancer (%)	Healthy children (%)
Age	Mean:9.44	Mean:9.49
Sex:		
Girls	38.9	
Boys	61.10	
Financial situation:		
High and middle income family	43.71	46.32
Low income family	56.29	53.68
Duration of disease	Mean: 3.4 years	-
Duration of hospital stay	Mean: 2 weeks	
Residency:		
Tehran	41.32	100
Other cities	58.68	

Table 2. Comparison of behavior and emotion problems between groups

Indexes	Group	X	SD	F statistic	P-value
DBD	Cases	31.46	24.58	263.82	0.00
	Control	25.73	21.06		
BDI	Cases	42.74	16.12	34.56	0.67
	Control	45.9	13.17		
CLI	Cases	10.76	33.38	197.55	0.00
	Control	6.48	38.87		
AS	Cases	72.51	12.69	27.79	0.74
	Control	79.26	16.31		

DBD= Disruptive Behavior disorder; BDI= Beck depression Inventory; CLI= Children's level of inhibition; AS= Anxiety disorder.

Table 3. MANOVA general F-test and Factors of behavior and emotion problems

Factor	F statistic	P- value	Eta squared
Age	47.76	0.65	0.17
Depression	92.18	0.00	0.041
Anxiety	113.56	0.00	0.56
Duration of disease	43.16	0.45	0.11
Duration of hospital stay	92.98	0.00	0.12
Financial situation	36.89	0.53	0.046

Table 4. Behavioral problems (disruptive behavior and inhibition) and gender in children with ALL

Dependent variables	Children with cancer			
	Girls		Boys	
	DBD	CLI	DBD	CLI
Depression	38.5 (.054)	3.2 (0.81)	43.21(0.3)	3.8(0.24)
Anxiety	44.6 (0.67)	3.5 (0.36)	40.7 (0.43)	3.1(0.67)
Age	35.4 (0.27)	2.6(0.12)	36.1(0.25)	2.3(0.04)
Duration of disease	31.7 (0.65)	2.3(0.45)	32.8(0.75)	2.2(0.74)
Duration of hospital stay	41.3 (0.73)	2.9 (0.09)	42.1(0.62)	2.7(0.69)
Financial situation	30.26(0.39)	2.4(0.9)	35.3(0.49)	2.5(0.62)

Note: data are M (SD), controlling for education status.

4. Conclusion

According to the findings of the present study, children with ALL displayed difficulties in some aspects of behaviors, especially in behavioral inhibitory. Studies have shown that children with cancer are susceptible to psychosocial disorders such as cognitive (Firoozi et al., 2011; Syrjala et al., 2011) and social deficits (Katz et al., 2011). Cognitive impairment as a side effect of chemotherapy in children with ALL, effects on flexibility of behavioral system. Abilities to retain, manipulate information, shift cognitive set, and quality of mental processes appear to be related to behavioral outcomes.

We can explain our results about the high rate of inhibitory in cases by Phipps' theory. "Repressive adaptive style" that Phipps (2007) brought forward showed that most of the children with cancer show high level of "repressive adaptive style" when compared to healthy children. Apparently, inhibition and repression of negative emotions are very similar. It is not correctly clear the reason for emotional and behavioral inhibition in children with cancer, but the results showed that the emotional consequences are positive.

Some considerable evidences emphasize neurobehavioral side effects in children receiving therapy for ALL. Cortisol rate plays an effective role in the behavioral system (Hsiao, et al., 2011). One of the side effects of the chemotherapy is cortisol suppression (Toppelbein et al., 2010). Previous studies demonstrated a nonlinear relation between cortisol level and disruptive behaviors. When cortisol level dramatically increases (in stressful situations) or decreases (as a side effect of treatment), behavioral problems have being bolded (Firoozi & Besharat, 2013). There are some evidences that declining cortisol level could associate with abnormality in glucose metabolism and the subsequent loss of energy. Locke of energy and vitality could lead to avoidance reactions in the cancer group.

Steroid therapy is the other treatment agent for ALL. The observed behavioral changes can be

confidently attributed to steroids. Findings suggest that during off-steroid weeks, behavior problems returned to baseline (Drigan et al., 1992).

According to the findings of this study, there was no discrepancy between cancer group and control in anxiety and depression. This may not seem surprising considering that numerous studies in the literature have reported findings indicating that children with cancer do not exhibit clinically significant symptoms of distress, and in fact, the report even lower levels of emotional disorders than control samples (Phipps et al., 2002). The numbers of researchers believe that children with cancer experience growth post stress and resiliency.

The findings of this study indicate that children with high anxiety and depression reveal more disruptive behavior disorder and behavioral inhibition. In addition, gender plays a moderating role in the relation between anxiety and depression to behavioral problems. It seems these participants have more biological preparedness for more severe inhibitory reactions. Also, The parents play an important role in the regulation of anxiety and depression. Mother's depression determines the child's mood (Robinson et al., 2007). When the mother is under stress and cannot control her behaviors and emotions, she succeeds in confusing her child in the same situation. The outcome of the study showed that, fundamental psychopathology in a mother with a child that is ill greatly affects the child's adaptation. Findings have shown that depression in mother positively correlated with anxiety and depression in child and negatively related to resiliency and vitality.

Likewise, contrary to our hypotheses, no statistically significant relation between "duration of disease and financial situation" and behavioral problems was observed. This result suggests the importance of mediators such as social support, psychological interventions and education in the hospital.

The data demonstrated there was very strong relation between duration of hospital stay and behavior

disruption in both of sex. Separation of friends and family, daily injection, limitation to movement and inability to control of the environment can explain this finding.

In contrast to some other studies, we found no evidence that age was associated with more significant behavioral disturbance. Perhaps the effects of chemotherapy on children are observed in the long term and severity of side effects depend on number of chemotherapy.

One of the limitations of this study was unavailability of information about stage of cancer, the roles of other factors influencing protocol of treatment in children with ALL should be evaluated.

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