ABSTRACT

Introduction: Despite achievements in treating acute lymphoblastic leukemia (ALL) in children, its burden on the psychosocial status of patients is not well defined yet. This study aims to determine the impact of childhood ALL on emotional and behavioral pattern of the patients compared to healthy peers as assessed by the Child Behavior Checklist (CBCL).

Methods: We studied 100 children with ALL (aged 6-12 years) and 100 healthy sex/age peers as control group. All ALL cases were treated by chemotherapy alone. After being informed by a psychologist, parents in both groups were asked to complete the CBCL form. Final results were then compared between the two study groups.

Results: There were no significant differences between the groups regarding the general characteristics. Failure in school performance, restricted group activity and less social relations were significantly higher in the ALL cases. Total competence was also significantly disturbed for the ALL cases. Social problems, attention problems, aggressive behavior, externalization, attention deficit/hyperactivity, conduct and oppositional defiant problems were significantly more prevalent in healthy children. Somatic problems were significantly higher in the ALL cases.

Conclusion: Our findings suggest that except for somatic problems, behavioral problems among the ALL cases are significantly less frequent than the healthy peers, which may stem from better care and support from the families. Our unique findings emphasize the need for more research on the psychosocial status of children with cancer in future.

KEYWORDS: Acute Lymphoblastic Leukemia; Behavioral Problem; Child Behavior Checklist; Childhood Cancer
of overall malignancies. However, the long-term survival rate of ALL has reached more than 80 percent in 1-10 year-old children and a majority of patients survive after treatment. Despite this great achievement, the impact of malignancies on the psychosocial qualities of children is yet to be understood.

Childhood malignancies can dramatically influence the psychosocial life of children and cause an involuntary change in the parents’ attitude toward treatment and education of their child. On the other hand, in children who are treated for ALL, the overall functional capacity and quality of life is lower than healthy children and they seem to have less satisfaction and comfort. Combination of these changes may lead to an unpleasant life style or future behavioral or psychosocial complications for the survivors. Depression, somatic distress, sleep disturbances, chronic fatigue syndrome, attention/concentration troubles, impaired auditory and visual short-term memory, reduced speed of processing, lower scores in global and verbal IQ’s and finally, learning disabilities are common neurocognitive manifestations due to both the disease and invasive treatment modalities like radiotherapy.

Combination of these changes may lead to an unpleasant life style or future behavioral or psychosocial complications for the survivors.

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Regarding the above mentioned points, this study aimed to investigate the effect of childhood ALL on the behavior and attention patterns of affected children who were treated with chemotherapy alone. We tested the hypothesis that children with ALL may suffer from more emotional/behavioral problems than their healthy peers.

METHODS
Study population
This case-control study was performed between March 2010 and March 2011 at Mofid Children Hospital, Tehran, Iran. Our study group consisted of 100 children with ALL and 100 healthy children as control (36 girls and 64 boys within each group). Patients were randomly selected from ALL cases who presented to our hospital and were treated and followed up there. We selected patients who were only treated by a similar conventional chemotherapy only and were in the remission phase of the disease at the time of enrolment. Patients who have been treated with radiotherapy were excluded. Our control group was randomly selected from 2 primary schools in the central Tehran. Subjects were matched for age, gender and school level. Next, parents of all subjects were asked to complete the study questionnaire after attending an introductory session.

Assessments
A socioeconomic status questionnaire was completed for each subject. This questionnaire included items about general characteristics of the child and parents. As the main assessment tool of this study, we used the latest standardized Persian version of the Child Behavior Checklist (CBCL) from the Achenbach System of empirically Based Assessment (ASEBA) designed for 6 to 18 year old children. CBCL/6-18 is a device by which parents or other caregivers of the child rate a child’s problem behaviors and competencies. This instrument was administered during an interview with the caregiver by a psychologist. The first part of the questionnaire consisted of 20 competence items and assessed the child’s level of social competence based on parents’ report of his/her involvement in social activities, such as hobbies, sports, jobs or team roles and activities. The CBCL includes 3 subscales assessing the child’s competency in three domains: activities, social interactions and school. The combination of these scores creates a total Social Competence Composite score. Higher scores indicate more social involvement of the child.

The second part of the questionnaire consisted of 113 items on behavior or emotional problems during the past 6 months. The parents were asked to rate “how true” the behavior is of their child. It yields eight behavioral subscales: withdrawn, somatic complaints, anxious/depressed, social problems, thought problems, attention problems, delinquent behavior, and aggressive behavior. Also, three behavioral composite scores are addressed: Internalizing Problems, Externalizing Problems, and Total Problems. Here, higher scores were indicative of more problems.
Data collection and Funding

Data collection in the case group was conducted in the oncology clinic at Mofid Children Hospital. For the control group, the forms were completed at school by the parents, following an introductory session. Each individual took 40-60 minutes to complete the form. All sessions were supervised by a psychologist.

The study protocol was reviewed and approved by the Research Board at Shahid Beheshti University of Medical Sciences and Payaam-e Noor University. The Central Educational Organization of Tehran granted the official permission to conduct the research. The present study was funded by Mofid Children Hospital and Shahid Beheshti University of Medical Sciences. Written informed consent was obtained from the parents of the participants and those who did not wish to take part were replaced.

Statistical methods

The statistical analyses of the questionnaire and checklist were conducted using SPSS (Statistical Package for the Social Sciences, Version 13.0). All the scores were classified and described, using standard charts and graphs. General characteristics are described as number, percentage, mean and standard deviation for each of the measurable variables. Variables with a normal distribution were tested with t-test and Man-Whitney test was used for variables without normal distribution. Chi-square or Fisher’s exact test were used for categorical variables. P value less than 0.05 was considered as significant.

RESULTS

Mean age in the ALL and control groups were 8.97±1.83 years and 8.74±1.74 years, respectively (p=0.36). Mean time since diagnosis in the ALL cases was 26 ± 7.67 months. There were no significant difference between the groups regarding age, gender, children’s level at school, parental level of study and mean family annual income. General characteristics of the study population and comparison between the two groups are presented in Table I.

| Variable                   | ALL (n=100)  | Healthy (n=100) | p-value |
|----------------------------|--------------|-----------------|---------|
| Age (year)                 | 8.97±1.83    | 8.74±1.74       | 0.36    |
| Gender (Male)              | 64           | 64              | -       |
| Child’s study level        | 0.06         |                 |         |
| Preschool                  | 15           | 13              |         |
| Primary school             | 71           | 83              |         |
| Secondary school           | 14           | 4               |         |
| Father’s educational level | 0.09         |                 |         |
| Secondary school graduate  | 20           | 11              |         |
| High school diploma        | 34           | 30              |         |
| College degree             | 45           | 57              |         |
| Mother’s educational level | 0.11         |                 |         |
| Primary school graduate    | 14           | 9               |         |
| High school diploma        | 44           | 45              |         |
| College degree             | 42           | 46              |         |
| Mean family annual income  | 101.3±2.9    | 105.5±1.2       | 0.09    |

* P<0.05 was considered as significant

In the comparison of the CBCL results for competence and adaptive performance scales, the ALL group had a significantly diminished school performance, group activity and social relations (Table 2). Total competence was also significantly disturbed for ALL cases (p<0.001). In the experience-based scales, scores for anxious/depressed condition, social problems, attention problems, aggressive behavior and externalizing behaviors were significantly higher in the healthy peers that indicated more behavioral problems in the healthy children rather than ALL cases. The mean score for somatic complaints were significantly higher in ALL cases (p=0.01). There was no significant difference between the groups regarding thought problems, delinquent behavior, and internalizing behaviors. Total problem scale significantly showed less clinical problems in the ALL cases (p=0.01). DSM-oriented scales were significantly different between the groups, except for anxiety problems. Somatic problems were significantly higher in the ALL cases (p<0.001).
Attention deficit/hyperactivity problem were significantly more frequent in healthy children (p<0.001). Similarly, significant differences were observed for oppositional defiant and conduct problems (p=0.002 and p<0.001, respectively).

Table-II: Comparing the results of CBCL between the groups, based on the t- scores.

| Scales                                      | ALL children          | Healthy children | P-value*   |
|---------------------------------------------|-----------------------|------------------|------------|
| Competence and adaptive performance scales  |                       |                  |            |
| Activity, (median [IQR])                    | 6.00 [3.00-7.00]      | 10.6 [7.00-46.2] | <0.001     |
| Social Relations, median [IQR]              | 1.00 [1.00-1.00]      | 6.50 [4.00-38.0] | <0.001     |
| School Performance, (mean ± SD)             | 33.29 ± 10.95         | 54.92 ± 16.77    | <0.001     |
| Total Competence, (median [IQR])            | 20.50 [12.40 – 34.80] | 53.8 [43.65-69.0] | <0.001     |
| Experience-based scales                     |                       |                  |            |
| Anxious / Depressed, (mean ± SD)            | 34.98 ± 21.32         | 48.43 ± 26.75    | <0.001     |
| Withdrawn/Depressed, (mean ± SD)            | 56.21 ± 26.99         | 48.68 ± 26.88    | 0.07       |
| Somatic complaints, (mean ± SD)             | 68.36 ± 27.44         | 54.22 ± 29.66    | 0.01       |
| Social problems, (mean ± SD)                | 39.12 ± 25.14         | 49.42 ± 25.87    | 0.005      |
| Thought problems, (mean ± SD)               | 55.67 ± 24.34         | 55.95 ± 26.43    | 0.93       |
| Attention problems (median [IQR])           | 29.50 [14.2 – 65.2]   | 46.20 [28.00-80.25] | 0.01     |
| Delinquent behavior (median [IQR])          | 65.20 [25.00-78.00]   | 50.00 [25.00-78.00] | 0.78      |
| Aggressive behavior, (mean ± SD)            | 38.84 ± 27.49         | 54.28 ± 28.24    | <0.001     |
| Internalizing behavior, (mean ± SD)         | 54.49 ± 24.15         | 52.39 ± 28.55    | 0.57       |
| Externalizing behavior, (mean ± SD)         | 44.87 ± 23.37         | 55.09 ± 27.91    | 0.005      |
| Total problems, (mean ± SD)                 | 50.97 ± 19.62         | 59.22 ± 27.92    | 0.01       |
| DSM-oriented scales                         |                       |                  |            |
| Affective Problems, (mean ± SD)             | 67.52 ± 15.87         | 53.18 ± 25.67    | <0.001     |
| Anxiety Problems, (mean ± SD)               | 49.76 ± 27.47         | 55.88 ± 28.49    | 0.12       |
| Somatic problems, (mean ± SD)               | 75.41 ± 25.16         | 55.76 ± 25.55    | <0.001     |
| Attention Deficit / Hyperactivity Problems, (mean ± SD) | 33.07 ± 20.11         | 48.94 ± 29.13    | <0.001     |
| Oppositional Defiant Problems, (mean ± SD)  | 46.87 ± 22.86         | 57.70 ± 26.35    | 0.002      |
| Conduct Problems (median [IQR])              | 25.00 [22.00-25.00]   | 25.00 [22.00-81.00] | <0.001      |

* P<0.01 was considered as significant; t-test is used for variables with normal distribution and Mann-Whitney test for variables that are not normally distributed.

ALL: Acute Lymphoblastic Leukemia; DSM: Diagnostic and statistical manual (of mental disorders); IQR: Interquartile range; SD: Standard deviation.

DISCUSSION

In the present study, we compared the behavioral and educational functioning of ALL cases and healthy children aged 6-12 years. Our findings indicated a significant reduction in the competence and adaptive performance scales among ALL cases. Surprisingly, behavioral problems were significantly higher in healthy peers. We also observed that anxious/depressed behaviors, social problems, attention problems, aggressive behavior and externalizing behaviors were significantly more frequent among healthy children, as well as attention deficit/hyperactivity conditions, conduct
and oppositional defiant problems regarding DSM-oriented scales. Somatic problems were more common in ALL cases. The latter finding can be rationalized as a consequence of the disease.

Childhood malignancies can influence one’s life and create behavioral and mental changes through time, apart from influencing physical growth and development. Therefore, childhood malignancies can reduce the quality of life and functional capacity of the affected children in comparison to their healthy peers, even in their future’s life.

CBCL is a good behavioral assessment tool in children that covers different psychological aspects of a child’s life. Most studies that used CBCL in children with chronic diseases have suggested no or slightly significant disturbances in the behavioral scales and DSM-oriented scales. Behavioral symptoms and psychological problems, including depression, in the leukemic patients following bone marrow transplantation are shown to be reversible after 2 years. However, lack of a control group in that study makes the interpretation difficult. A cross-sectional study just showed a slight reduction in the externalizing behaviors, without any extra emotional or behavioral symptoms in children with ALL. Increased risk of behavioral and educational problems was reported in children with malignancy. However, the pattern of problems in the present study is slightly different from the previous ones.

Our study shows unique results of fewer behavioral problems in ALL cases. To the best of our knowledge, other studies have mostly reported a higher incidence of behavioral problems in children with malignancy. For instance, one study showed that cancer survivors were 1.5 and 1.7 times more likely than their siblings to have symptoms of depression/anxiety and antisocial behaviors, respectively. Nonetheless, this survey includes different types of cancer, especially brain tumors and particularly patients who were treated by radiotherapy. Therefore, the results may have been confounded due to the influential factors of each cancer. We suppose that influential factors such as socioeconomic status and the culture of the study population can affect the result of each survey, let alone the biological characteristics and pathophysiology of the malignancy that might even interfere with the neurocognitive maturation. In the Iranian Society, the family core is strong and particularly having sick children in the family will result in a stronger family relations and support. Therefore, the sick child will be supported much more than a healthy child and this may result in a better psychological status with less emotional/behavioral defects.

Also, the treatment modality can play an important role in this regard. Patients who have been received CNS-directed therapy for malignancy are mostly at high risk of cognitive and behavioral problems. The magnitude of these problems is so high that necessitates pharmacological treatment with agents like methylphenidate for attention deficit. Therefore, risk stratification and diagnosis based on the natural history of the malignancy and treatment modality is necessary for any further decision. In this study, we excluded patients who received therapeutic modalities extra than chemotherapy. Therefore, these findings can be attributable to both the natural history of ALL and sequel of chemotherapy. One study have shown that the approximately 76% and 19% of the adolescent survivors of pediatric cancer have behavioral and emotional problems, respectively. Therefore, the psychological effect of the disease may appear later than the course of the disease and this necessitates studies on the emotional/behavioral problems of cancer survivors. Results of the present study could be a cornerstone for future investigations on psychological evaluations in childhood malignancies. It may also help for designing a better psychological consultation plan for the parents of children with malignancy.

Limitations

The validity of questionnaires is important in scientific research. This is mostly influenced by the socioeconomic status of the responders and it is unavoidable. We tried to recruit patients who were only treated with chemotherapy and were in the remission phase. Importantly, all patients were in the remission phase, receiving maintenance therapy. Single center selection of the patients helped much, although patients lived in different areas of the city. The strength of this study is
selecting healthy peers, matched for age and gender, as a control group.

CONCLUSION

This study showed a reduction in functional capacity and more somatic problems in the children with ALL compared to the healthy peers. Conversely, behavioral problems were more in the healthy peers. We presume that better care and support from the families of the affected children may result in a better emotional/behavioral status of children with ALL. The findings of this study may help the researchers to recognize the need for diagnosing real behavioral problems and main psychological issues in children with malignancy.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

REFERENCES

1. Basta NO, James PW, Gomez-Pozo B, Craft AW, McNally Rj. Survival from childhood cancer in northern England, 1968-2005. Br J Cancer. 2011; 105:1402-8.
2. Savage E, Riordan AO, Hughes M. Quality of life in children with acute lymphoblastic leukemia: a systematic review. Eur J Oncol Nurs. 2009;13:36-48.
3. Ribera JM, Oriol A, Sanz MA, Tormo M, Fernandez-Abellan P, del Potro E, et al. Comparison of the results of the treatment of adolescents and young adults with standard-risk acute lymphoblastic leukemia with the Programa Espanol de Tratamiento en Hematologia pediatric-based protocol ALL-96. Journal of Clinical Oncology. 2008; 26:1843-9.
4. Pui CH. Toward a total cure for acute lymphoblastic leukemia. Journal of Clinical Oncology. 2009; 27:5121-3.
5. Lucia A, Ramirez M, San Juan AF, Fleck SJ, Garcia-Castro J, Madero L. Intrahospital supervised exercise training: a complementary tool in the therapeutic armamentarium against childhood leukemia. Leukemia. 2005; 19:1334-7.
6. San Juan AF, Chamorro-Vina C, Mate-Munoz JL, Fernandez del Valle M, Cardona C, Hernandez M, et al. Functional capacity of children with leukemia. Int J Sports Med. 2008;29:163-7.
7. Caprino D, Wiley Tj, Massimo L. Childhood cancer survivors in the dark. Journal of Clinical Oncology. 2004; 22:2748-50.
8. Leung W, Hudson MM, Strickland DK, Phipps S, Srivastava DK, Ribeiro RC, et al. Late effects of treatment in survivors of childhood acute myeloid leukemia. Journal of Clinical Oncology. 2000; 18:3273-9.
9. Schultz KA, Ness KK, Whitton J, Recklitis C, Zebrack B, Robison LL, et al. Behavioral and social outcomes in adolescent survivors of childhood cancer: a report from the childhood cancer survivor study. Journal of Clinical Oncology. 2007; 25:3649-56.
10. von der Weid NX. Adult life after surviving lymphoma in childhood. Support Care Cancer. 2008; 16:339-45.
11. Dejong M, Fombonne E. Depression in paediatric cancer: an overview. Psychooncology. 2006; 15:553-66.
12. Shahrivar Z, Shirazi E, Yazdi AB, Alghband-rad J. Validity of the Child Behavior Checklist-Persian Version in a Community Sample of Iranian Youths. Iranian Journal of Psychiatry and Behavioral Sciences. 2011; 5:45-9.
13. Achenbach TM. Manual for the child behavior checklist/4-18 and 1991 profile. Burlington, VT: Dept. of Psychiatry, University of Vermont; 1991.
14. Achenbach TM, Rescorla L. Manual for the ASEBA preschool forms & profiles : an integrated system of multi-informant assessment. Burlington, Vt.: ASEBA; 2000.
15. Langeveld NE, Stam H, Grootenhuis MA, Last BF. Quality of life in young adult survivors of childhood cancer. Support Care Cancer. 2002; 10:579-600.
16. Zebrack BJ, Zeltzer LK, Whitton J, Mertens AC, Odom L, Berkow R, et al. Psychological outcomes in long-term survivors of childhood leukemia, Hodgkin's disease, and non-Hodgkin's lymphoma: a report from the Childhood Cancer Survivor Study. Pediatrics. 2002; 110:42-52.
17. Campbell LK, Scaduto M, Van Slyke D, Niarhos F, Whitlock JA, Compas BE. Executive function, coping, and behavior in survivors of childhood acute lymphocytic leukemia. J Pediatr Psychol. 2009; 34:317-27.
18. Noll RB, MacLean WE, Jr., Whitt JK, Kaleita TA, Stehbens JA, Waskerwitz MJ, et al. Behavioral
adjustment and social functioning of long-term survivors of childhood leukemia: parent and teacher reports. J Pediatr Psychol. 1997; 22:827-41.

19. Michalowski M, Ketzer C, Daudt L, Rohde LA. Emotional and behavioral symptoms in children with acute leukemia. Haematologica. 2001; 86:821-6.

20. Sawyer M, Crettenden A, Toogood I. Psychological adjustment of families of children and adolescents treated for leukemia. Am J Pediatr Hematol Oncol. 1986; 8:200-7.

21. Barrera M, Atenafu E, Pinto J. Behavioral, social, and educational outcomes after pediatric stem cell transplantation and related factors. Cancer. 2009; 115:880-9.

22. Liang HF, Chiang YC, Chien LY, Yeh CH. A comparison of emotional/behavioral problems between Taiwanese children with cancer and healthy controls. J Clin Nurs. 2008; 17:304-11.

23. Dolson EP, Conklin HM, Li C, Xiong X, Merchant TE. Predicting behavioral problems in craniopharyngioma survivors after conformal radiation therapy. Pediatr Blood Cancer. 2009; 52:860-4.

24. Wolfe-Christensen C, Mullins LL, Scott JG, McNall-Knapp RY. Persistent psychosocial problems in children who develop posterior fossa syndrome after medulloblastoma resection. Pediatr Blood Cancer. 2007; 49:723-6.

25. Buizer AI, de Sonneville LM, van den Heuvel-Eibrink MM, Veerman AJ. Behavioral and educational limitations after chemotherapy for childhood acute lymphoblastic leukemia or Wilms tumor. Cancer. 2006; 106:2067-75.

26. Lofstad GE, Reinjell T, Hestad K, Diseth TH. Cognitive outcome in children and adolescents treated for acute lymphoblastic leukaemia with chemotherapy only. Acta Paediatr. 2009; 98:180-6.

27. Rey-Casserly C, Meadows ME. Developmental perspectives on optimizing educational and vocational outcomes in child and adult survivors of cancer. Dev Disabil Res Rev. 2008; 14:243-50.

28. Utens EM, Verhulst FC, Duivenvoorden HJ, Meijboom FJ, Erdman RA, Hess J. Prediction of behavioural and emotional problems in children and adolescents with operated congenital heart disease. Eur Heart J. 1998; 19:801-7.

29. Mulhern RK, Butler RW. Neurocognitive sequelae of childhood cancers and their treatment. Pediatr Rehabil. 2004; 7:1-14; discussion 5-6.

30. Conklin HM, Reddick WE, Ashford J, Ogg S, Howard SC, Morris EB, et al. Long-term efficacy of methylphenidate in enhancing attention regulation, social skills, and academic abilities of childhood cancer survivors. J Clin Oncol. 2010; 28:4465-72.

31. Kahalley LS, Wilson SJ, Tyc VL, Conklin HM, Hudson MM, Wu S, et al. Are the psychological needs of adolescent survivors of pediatric cancer adequately identified and treated? Psychooncology. 2013; 22:447-58.