

Emotional and behavioral symptoms in children with acute leukemia

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Background and Objectives. The diagnosis of leukemia is probably one of the most severe stressors that children can experience and may be associated with emotional and behavioral symptoms indicating comorbidity with mental health disorders. This study aims to evaluate the presence of emotional and behavioral symptoms in children with acute leukemia exposed to chemotherapy from outpatient services at two university hospitals in Brazil.

Design and Methods. In this cross-sectional study, emotional and behavioral symptoms were assessed using the Child Behavior Checklist (CBCL) in three groups of children aged 5–14 years: a) children with acute leukemia (n = 21); b) children with blood dyscrasias (n = 21); c) children evaluated or treated in a pediatric outpatient service (n = 33).

Results. Children with blood dyscrasias had significantly fewer symptoms of externalization (delinquent and aggressive behavior) than pediatric controls ($p < 0.05$). Children with leukemia did not differ from the two other groups regarding symptoms of externalization. No significant difference on the scores of the CBCL internalization dimension (anxiety, depression, somatic symptoms and withdrawal) was found among the three groups.

Interpretation and Conclusions. These findings seem to indicate that children with acute leukemia do not have more emotional or behavioral symptoms than children with benign hematologic or physical diseases suggesting that comorbidity with mental disorders is not higher in children with acute leukemia than in children in the other two groups.

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Key words: leukemia, children, mental health, behavioral symptoms, emotional symptoms.

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Some previous reports indicated that one in every 1,000 adults between 20–29 years of age in the US would be a survivor of childhood malignancies in the beginning of the new millennium as a result of improvements in chemotherapy and radiotherapy. So, nowadays, not only curing the disease but also causing the smallest possible damage to the long-term life of these individuals must be emphasized.^{1,2} Leukemia is one of the most common childhood cancers and has been a focus of constant medical attention and research. It tends to be a chronic rather than a terminal illness, with a high cure rate.^{3,4}

The diagnosis of a malignant disease is probably one of the most severe stressors that children and parents can experience.⁵ This may change patients' personality and their relationships with family.⁶⁻⁸ Even how the child gets to know about his or her disease may have a different impact on behavior and psychosocial adjustment.⁸ Moreover, children suffer many different acute mental changes (seizures, encephalopathy) related to their own disease or to the highly toxic drugs used during treatment that may cause emotional and behavioral consequences not yet completely known.⁹⁻¹¹ Concurring with these pieces of evidence, previous studies suggested that childhood cancer had a significant adverse impact on the mental health of children and their families.^{3,7,12,13} However, other recent reports did not observe significant differences in emotional and behavioral problems that could indicate mental health disorders between patients with cancer and their families and community controls.¹⁴⁻¹⁷ In addition, Canning *et al.*¹⁸ found that most children with cancer use a repressive style of adaptation and report less depressive symptoms than a control group of school children.

Some limitations in the previous studies may explain the conflicting findings reported in the literature. The samples of children with cancer often vary greatly in age, in the length of time since their can-

cer was diagnosed and in the type of cancer included. Moreover, the majority of the previous studies did not have a control group¹² or compared children with cancer against community controls instead of comparing them against children with other benign hematologic diseases and/or against pediatric controls.^{3,7,13,15-18} Since it is well-established that children referred to a tertiary hospital have more psychiatric problems than community controls, independently of their diagnosis, the effect of a referral bias on the differences in emotional and behavioral problems between leukemia inpatients/outpatients and community controls was not adequately considered in previous studies.

The present study aims to evaluate the presence of emotional and behavioral symptoms in children with acute leukemia exposed to chemotherapy at two university hospitals in Brazil. Based on the literature, we hypothesized that: 1) children with acute leukemia exposed to chemotherapy will present similar emotional and behavioral problems as children with benign blood dyscrasias; b) children with acute leukemia exposed to chemotherapy will present more emotional and behavioral problems than children from a pediatric outpatient clinic.

Design and Methods

In this cross-sectional study, the sample groups were enrolled from two university hospitals in Porto Alegre, Brazil. Porto Alegre is the capital of Brazil's southernmost state and has 1,400,000 inhabitants.

Subjects

The sample comprised three groups: 1) the acute leukemia group (LG) – all children aged 5 to 14 years with acute leukemia in treatment for a minimum period of 4 months and a maximum period of 36 months in the outpatient hematologic divisions of the Hospital de Clínicas de Porto Alegre (HCPA) and the Hospital da Criança Santo Antônio (HCSA); 2) a blood dyscrasia group (BDG) – all children aged 5 to 14 years with benign blood dyscrasias in treatment for a minimum period of 4 months and a maximum period of 36 months at HCPA; 3) a pediatric control group (CG) – a group of children aged 5 to 14 years with none of the pathologies mentioned above was randomly selected from the pediatric outpatient clinic at the HCPA. The only exclusion criterion in the study was the presence of congenital anomalies.

Procedures

The Child Behavior Checklist (CBCL) was selected for the evaluation of children's behavior and emotional symptoms. The CBCL is a widely used behavioral and emotional symptom checklist for children

from 4 to 18 years of age that records 112 child emotional and behavioral problems and 3 areas of competency as reported by parents. The instrument derives a total problems' score and the symptoms are also clustered into two dimensions: externalizing (delinquent and aggressive behavior) and internalizing (anxiety, depression, somatic symptoms and withdrawal).^{19,20} The CBCL shows good convergence with structured interviews for psychiatric diagnosis in children²¹ and extensive information is available about its reliability and validity.²⁰ The CBCL has been translated into 55 languages. Recently, Crijnen *et al.*²² demonstrated that the CBCL is a robust instrument for assessing problems of children when used cross-culturally in 12 different countries. The CBCL had been previously translated into Portuguese, and its concurrent validity evaluated for Brazilian children.²³ Moreover, the CBCL is the most used instrument for the evaluation of emotional and behavioral symptoms in previous investigations with leukemia children.^{3,7,13,24,25} Although the CBCL is a self-administered instrument, trained research assistants helped the parents to complete the instrument to avoid assessment bias. This procedure was conservatively chosen, since the parents of our sample were from low income families with low educational level.

Information about socio-demographic data was systematically collected from the parents. The project was approved by the Ethical Committee of the Hospital de Clínicas de Porto Alegre and informed consent was requested from all parents.

Data analysis

The comparison of all categorical variables among the three groups was performed using the χ^2 test.²⁶ A significance level of 5% was accepted in these comparisons. Since the great majority of continuous data did not show a normal distribution, non-parametric tests were used in these analyses (Kruskal-Wallis one-way Anova). Scores on scales of the CBCL were compared among groups using the raw data.²⁰ When a difference was found among the three groups, non-parametric multiple comparison tests were performed to detect which groups were different.²⁷ In these post-hoc analyses, a significance level of 5% was also accepted.

Results

The sample comprised 75 children, 21 in the leukemia group (LG), 21 in the blood dyscrasias group (BDG) and 33 in the pediatric control group (CG). There were no sample losses, since all invited parents agreed to participate in the study and completed the CBCL. The median age in the LG was 7

Table 1. Demographic characteristics and duration of treatment among groups.

Characteristics*	Groups		
	Leukemia (n=21)	Blood Dyscrasia (n=21)	Pediatric Controls (n=33)
Age (years) °	7 (4-14)	8 (4-11)	8 (5-13)
Sex (male)°	11 (52.4)	8 (38.1)	14 (42.4)
Race (Caucasian)°	18 (85.7)	18 (85.7)	26 (78.8)
Monthly family income (per family member)°:			
≥ US 53	6 (28.6)	6 (28.6)	19 (57.6)
< US 53†	15 (71.4)	15 (71.4)	14 (42.4)
Mother's educational level (uncompleted elementary school) °	7 (33.3)	13 (61.9)	15 (45.5)
Father's educational level (uncompleted elementary school)°	11 (52.4)	11 (52.4)	14 (42.4)
Duration of treatment (months)°	6 (4-33)	8 (4-34)	33 (1-108)

*Median and range (in parentheses) are reported for continuous variables; n and percent (in parentheses) are reported for categorical variables; ° difference among groups was not significant ($p > 0.05$); †cut-off point frequently used to define poverty in Brazil; ‡difference among groups was significant ($p = 0.006$). At post-hoc analysis, significant differences were found between leukemia and control groups ($p < 0.05$), and between blood dyscrasia and control groups ($p < 0.05$).

years (range: 4-14 years), 52% of the children in this group were male and 86% were Caucasians. The median duration of treatment for leukemia children was 6 months (range: 4-33 months). There were no significant differences regarding age, sex, race, family income, and parents' educational level among groups. The only significant difference found was in the duration of treatment (Kruskal-Wallis = 10.13; d.f. = 2; $p = 0.006$). At post-hoc analysis, significant differences were localized between LG and CG ($Q = 2.7$; $p < 0.05$) and between BDG and CG ($Q = 2.7$; $p < 0.05$) (Table 1).

The main diagnoses in the BDG were: idiopathic thrombocytopenic purpura (43%), iron deficiency anemia (14%), von Willenbrand's disease (10%), and hereditary spherocytosis (10%). The majority of subjects in the CG were healthy children who had come to the pediatric outpatient clinic for regular checkups (40%). The main medical problems in the CG were obesity (15%), hepatitis (9%), undernutrition (6%), and otitis (6%). No child with any type of cancer was included in the pediatric control group.

There was no significant difference in the total problem score of the CBCL among the three groups (Kruskal-Wallis = 5.74; d.f. = 2; $p = 0.57$) (Figure 1). Also, no significant difference was found in the CBCL internalization dimension scores (anxiety, depression,

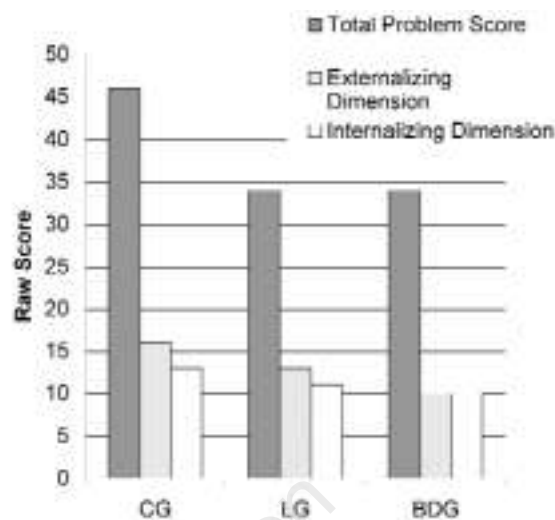


Figure 1. Median CBCL scores among groups. CG = pediatric control group; LG = leukemia group; BDG = blood dyscrasia group. A significant difference in externalization symptoms was found among groups ($p < 0.05$). > = indicates which group was different ($p < 0.05$) from the others at post-hoc analysis.

somatic symptoms and withdrawal) among groups (Kruskal-Wallis = 0.92; d.f. = 2; $p = 0.63$). To investigate depressive and anxiety symptoms in detail, we checked the prevalence of symptoms included in the CBCL anxious/depressive scale individually in the three groups. Again, no significant difference was found in any depressive or anxiety symptom evaluated among groups ($p > 0.05$) (Table 2).

A significant difference was detected in the externalization dimension of the CBCL (delinquent and aggressive behavior) among groups (Kruskal-Wallis = 9.45; d.f. = 2; $p = 0.009$). At post-hoc analysis, the difference was found between the BDG and CG ($Q = 3.04$; $p < 0.01$). Children in the blood dyscrasia group had significantly lower scores in the externalizing dimension than children from the pediatric control group. No significant differences were found between the BDG and LG ($Q = 1.27$; $p = \text{NS}$) or between the LG and CG in the externalizing dimension of the CBCL ($Q = 1.64$; $p = \text{NS}$) (Figure 1).

Discussion

In a sample of Brazilian children from two university hospitals, children with acute leukemia did not have more emotional or behavioral problems than either children with benign blood dyscrasia or children from a pediatric outpatient clinic. To the best

Table 2. Anxiety and depressive symptoms among groups.

Characteristics*	Groups		
	Leukemia (n=21)	Blood Dyscrasia (n=21)	Pediatric Controls (n=33)
Frequent complaints of loneliness	1 (4.8)	3 (14.3)	6 (18.2)
Cries a lot	2 (9.6)	0 (0)	9 (27.3)
Frequent fear of thinking or doing something bad	4 (19)	4 (19)	5 (15.2)
Frequently feels that has to be perfect	6 (28.6)	7 (33.3)	8 (24.2)
Frequently feels that no-one loves him/her	1 (4.8)	0 (0)	8 (24.2)
Frequently feels others are out to get him/her	1 (4.8)	0 (0)	2 (0.6)
Frequently feels worthless	0 (0)	0 (0)	1 (0.3)
Frequently nervous or tense	6 (28.6)	2 (9.5)	12 (36.4)
Frequently fearful or anxious	2 (9.5)	0 (0)	3 (9.1)
Frequently feels too guilty	2 (9.5)	0 (0)	2 (0.6)
Frequently self-conscious or easily embarrassed	2 (9.5)	2 (9.5)	3 (9.1)
Frequently suspicious	5 (23.8)	0 (0)	4 (12.1)
Frequently unhappy or sad	2 (9.5)	0 (0)	4 (12.1)
Frequently worried	3 (14.3)	1 (4.8)	3 (9.1)

*Anxiety and depressive symptoms included in the anxious/depressive scale of the Children Behavior Checklist. No significant difference in any symptom was found among groups ($p > 0.05$); n and percent (in parentheses) are reported.

of our knowledge, this is the first study evaluating emotional and behavioral symptoms in children with acute leukemia from a culture outside the US or other developed country. Also, this is one of the first studies comparing leukemic children against referred instead of community controls.

Our findings demonstrating that children with acute leukemia did not have more externalizing (behavioral) problems than either children with benign hematologic diseases or those with medical problems concur with previous reports.^{3,13,28,29} Sawyer *et al.*¹³ did not find a significant difference in behavioral problems (scores in the externalizing dimension of the CBCL) between 38 cancer children and 39 control youths from the community. Considering that cultural factors may modulate the clinical manifestation of behavioral disorders,³⁰ our findings seem to suggest that children with acute leukemia do not present more externalizing problems than other children even in a Latin culture in which emotional distress is frequently manifested through behavioral symptoms.

The significant difference found in externalizing symptoms between children with blood dyscrasias and pediatric controls in our sample was an unexpected finding. Children with blood dyscrasias had fewer externalization symptoms than pediatric controls. Although the reasons for this difference in our study remain unknown, pediatric patients from university tertiary centers normally have high frequencies of behavioral symptoms and children with hematologic diseases may be less adept at externalizing symptoms because of limitations imposed by the disease and the treatment (hospitalizations,

physical restrictions). If so, this fact could explain the difference found. Nevertheless, the small difference found in the median scores of the CBCL externalizing dimension between blood dyscrasia children and those from the pediatric clinic (6 points), although statistically significant, may not reflect a clinically significant difference.

We were not able to find any significant difference regarding scores in the internalization dimension of the CBCL among the three groups. Even when children's anxiety and depressive symptoms reported by parents were evaluated individually, significant differences did not appear among groups. Our results regarding emotional symptoms (anxiety, depression, somatic symptoms and withdrawal) are in agreement with part of the literature indicating that children with leukemia do not report more internalization symptoms than others.^{2,14,18} Trying to explain the lack of significant difference in internalization problems between children with cancer and community controls in their study, Canning *et al.*¹⁸ proposed that a repressive adaptive style, frequently found in children with cancer, makes them unable to show emotional symptoms. They suggest that this repressive style may be a long-term protector against psychological experiences or an adaptation to stress. Studies that found significantly more internalization symptoms in children with cancer^{3,13} used control groups with healthy children from the community, making any comparison with our findings difficult. Moreover, even the higher scores in the internalizing dimension of the CBCL found in leukemia children at the moment of the diagnosis in

the study by Sawyer *et al.*¹³ tended to decrease significantly when symptoms were re-evaluated 1 and 2 years after the diagnosis. Thus, studies that detected a difference in internalization problems between leukemia children and community controls may be demonstrating only a transitory phenomenon.

Our results must be understood in the context of some limitations. Although the CBCL shows good convergence with structured interviews for psychiatric diagnosis in children²¹ and extensive information is available about its reliability and validity,²⁰ only this screening instrument was used for the evaluation of behavior and emotional problems. However, paper and pencil checklists such as the CBCL are fast to apply, economical and easily accessible for the non-mental health clinician, being able to predict the possible categorical diagnosis with reasonable certainty. Also, the use of parents as an information source may have created a report bias, since parents are not the best informants for internalization symptoms. However, this was the strategy used in the majority of previous studies, especially for children younger than 12 years of age. Finally, a type II error (small sample size) could have prevented the detection of a significant difference in internalization symptoms among groups and in externalization symptoms between children with leukemia and blood dyscrasias. However, the size of the differences among groups in these comparisons was very small indicating more similarities than differences regarding these dimensions of psychopathology.

Clinical implications

During the last decade, many investigations have been conducted in an attempt to detect possible psychological and social consequences of childhood cancer. As a result of the great improvement in treatment, nowadays, any patient with cancer is potentially curable and has a social life during and after treatment. Moreover, comorbidity with mental disorders (e.g., anxiety and depressive disorders) are not infrequent in patients with chronic physical illness.³¹ This fact increases the importance of mental health investigations that may give medical staff more information about how to deal with these patients. Thus, our findings can help pediatric hematologists to approach children with leukemia and their families better, suggesting that the presence of this severe disease does not necessarily mean that affected youths will suffer more mental health disorders than children with other benign physical conditions. However, it is important to emphasize that the absence of more emotional and behavioral problems that could suggest the presence of comorbid-

ity with mental health disorders in leukemia patients does not mean the absence of psychological distress and important emotional overload in these children and their families. Also, our findings indicating that leukemia children are not at higher risk of mental disorders than children with other benign physical conditions do not exclude the possibility that some children with leukemia may suffer from important mental health disorders, such as depression. Thus, pediatric hematologists should be prepared to give emotional support to patients with leukemia and their families in the context of a good patient-physician relationship and also to refer some of them for psychiatric evaluation if important behavioral and emotional symptoms are detected.

Despite the caveats mentioned, our findings seem to suggest that children with acute leukemia do not have more emotional and behavioral problems that could suggest comorbidity with mental health disorders than either children with benign hematologic diseases or children from a pediatric outpatient clinic. More follow-up studies from different cultures and including the evaluation of family members are needed.

Contributions and Acknowledgments

MM conceived the project, actively participated in data collection and the data analysis process, and prepared the first draft of the manuscript. CK revised the literature on mental health and acute leukemia, actively participated in data collection and the data analysis process and helped in the preparation of the first draft of the manuscript. The two senior authors worked as advisors in child hematology (LD) and child psychiatry (LAR) during all steps of the project. They actively revised the manuscript for publication.

Disclosures

Conflict of interest: none.

Redundant publications: a preliminary version of this study was presented in the research poster session of the 46th annual meeting of the American Academy of Child and Adolescent Psychiatry, Chicago, 1999, and in the poster section of the Fourth Congress of the European Haematology Association, Barcelona, 1999.

Manuscript processing

This manuscript was peer-reviewed by two external reviewers and by Professor Giuseppe Masera, who acted as an Associate Editor. The final decision to accept this paper for the publication was taken jointly by Prof. Masera and the Editors. Manuscript received March 21, 2001; accepted June 26, 2001.

Potential implications for clinical practice

To help pediatric hematologists to approach children with leukemia and their families better, clarifying that the presence of this severe disease does not necessarily mean that affected children will suffer more psychological problems than children with other benign medical conditions.

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