

Depressive symptomatology in children with acute lymphoblastic leukemia

Sintomatologia depressiva em crianças com leucemia linfóide aguda

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RESUMO

Objetivos: Investigar a gravidade da sintomatologia depressiva em uma população de crianças Brasileiras com a leucemia linfoblástica aguda (LLA)

Métodos: A amostra foi composta por 31 crianças diagnosticadas com LLA e 31 controles, com idades entre 6 e 15 anos de idade, recrutadas em uma unidade de oncologia pediátrica, em Recife-Pernambuco (Brasil). Foi utilizada a *Children depression inventory-CDI* e a *Depression children's rating scale - revised – CDRS-R* para avaliar a sintomatologia depressiva

Resultados: Encontramos mais sintomatologia depressiva nos grupos de pacientes usando a CDRS-R (U=192.0; p<.0001), mas não houve diferença significativa com a aplicação da CDI (U= 47.0, n.s).

Conclusão: Uma maior severidade dos sintomas depressivos em crianças com LLA, detectada pela CDRS-R, sugerindo uma baixa aplicabilidade da CDI, particularmente nesta população. Estes resultados são comparados com a literatura vigente.

Palavras-chave : Depressão Infantil, Câncer, Crianças, Sintomatologia depressiva, LLA.

ABSTRACT

Objectives: To investigate the severity of the depressive symptomatology in a population of Brazilian children with acute lymphoblastic leukemia (ALL)

Methods: The sample was compound by 31 children with diagnosis of acute lymphoblastic leukemia (ALL) and 31 controls, with age range between 6-15 years old, recruited in a major pediatric oncology unit in Recife, Pernambuco (Brazil). We used the *Children depression inventory-CDI* and the *Depression children's rating scale - revised – CDRS-R*. to evaluate depressive symptomatology.

Results: We found higher scores of depressive symptomatology in the patient's group using the CDRS-R (U=192.0; p<.0001), but there was no significant difference when applying the CDI (U= 47.0, n.s).

Conclusions: A greater severity of depressive symptoms were found symptomatology in children with ALL, showed by the CDRS-R and the suggesting a low utility of the CDI in this particular kind of population. The results are discussed and compared with the current literature.

Keywords: Children depression, Cancer, Children, Depressive symptomatology, ALL.

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INTRODUCTION:

There have been great advances in the treatment of acute lymphoblastic leukemia (ALL) in pediatric patients during the last twenty five years, and now around 60 % of them survive with complete remission for more than five years^{1, 15}. A growing body of multidisciplinary research in treatment of ALL is increasing the life expectation of these patients, allowing them to live longer, coping with stressful limitations caused by this chronic disorder and the treatment side effects¹.

Previous analysis showed a higher prevalence of depressive symptoms in children from pediatric cancer centers when compared to the general population^{12, 21}. However, more recent studies reported lower scores for depressive symptoms in children with cancer, especially when using self-assessment questionnaires to evaluate depressive symptomatology^{11,23,6,16,14}.

Notwithstanding the recent design of more specific scales to evaluate mood disorders in children and adolescents, there is a scarce number of studies including patients with specific kinds of cancer, such as ALL, especially regarding the simultaneous use of different methods to evaluate affective symptoms.

There is a current debate about the influence of the immune system in mood disorders such as major depression and dysthymia, and vice-versa.

This is part of a major effort to improve detection of children with this condition and eventually to provide a better assistance.

OBJECTIVES:

- The aim of our analysis is to qualify and quantify depressive symptoms in a population of Brazilian children with ALL, compared to a control group matched by gender and age, using a self-assessment scale and a semi-structured questionnaire with different formats.

- To compare the frequency of depressive symptomatology between the patient and control groups.

- To compare our results with the findings in populations of other countries.

- To compare the results obtained with a self-assessment scale and semi-structured questionnaire.

METHODS:

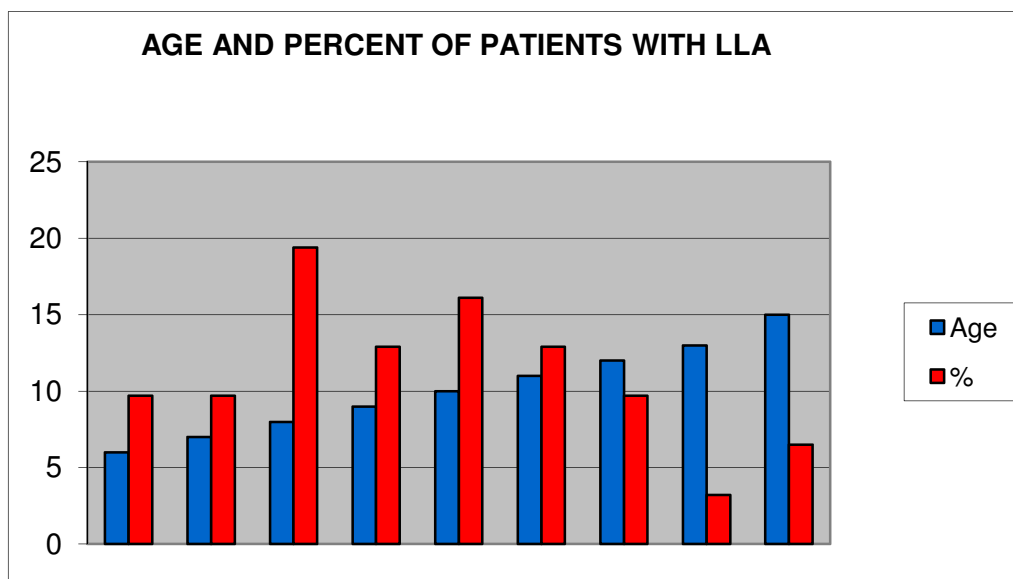
Study design:

This is a transversal analysis of depressive symptomatology in a group of patients with ALL compared with a group of controls subjects without ALL, matched by age and gender.

Affected Subjects:

We recruited thirty one pediatric patients diagnosed with ALL from the Unit of Hematology and Oncology of IMIP, 18 boys and 13 girls, and mean age of 9.55 years old (range of 6-15, SD=2.39). The figure 1 shows the number of patients through different groups of ages.

FIGURE 1. AGE AND PERCENT OF THE CHILDREN WITH ALL



The diagnostic criteria for ALL was based on the protocol "Total XIIIb from the St Jude Children Hospital".

The exclusion criteria was 1) Ages < 6 years old or > than 15 years old. 2) Previous psychiatric disease. 3) Children without ALL or with other types of cancer and chronic disorders. 4) Previous history of radiotherapy treatment. 5) Children not accompanied by their mothers. 5) Patients without clinical conditions to be interviewed. 6) Children without informed consent.

Control group:

This group of subjects without ALL (n=31), carefully matched by age and gender with the patient's group, was randomly recruited from a public school in Recife and submitted to the same inventory and clinical scales than the ALL group.

Scale and inventory:

Children's depression scale rating scale-reversed – CDRS-R²⁰ - This is a semi-structured interview covering 17 items to evaluate mood and behavior, including the DSM criteria for major

depression and dysthymia. This is an important and widely used reference for research in affective disorders in pediatric population^{5, 18}.

The children's depression inventory – CDI¹³

This questionnaire evaluates depressive symptomatology in children of ages between 6 and 17 years old, including 27 items that quantify a wide range of depressive symptoms, including mood changes, suicidal thoughts, appetite and sleep patterns. Each item has three possible answers (scores of 0-2), allowing a final total score of 54. This inventory was previously adapted and validated in a study with Brazilian children, defining a cut-off of 18⁷.

To make sure that both groups (patients and controls) have a similar social-demographic background we used the Occupational scale of Hollingshead in order to match occupational status of their parents¹⁰.

In our research protocol we also investigated previous history of chronic disorders, psychiatric conditions, family structure and usual behavior amongst the patients, controls and their parents. Other medical aspects (non psychiatric) of ALL were also evaluated in these subjects, including periods in awards (previously and during this investigation), class and phase of use of

chemotherapy drug used during treatment, onset of symptoms, etc.

Procedures:

This study was approved by the IMIP ethical committee and informed consent form were obtained from the patient’s parents. The scale and inventory were used by trained psychiatrists and psychologists under the supervision of the author (J.M.B).

The subjects were enrolled in the out patient program for chemotherapy and they were in different stages of treatment (induction or maintenance).

During this study the subjects were evaluated in one or two interviews, depending of the available time during each visit.

Statistical analysis:

We used the “Statistical Package for the Social Science – SPSS” MS WINDOWS, version 6.1.

To compare variable differences between patients and controls we used statistical algorithms such as “the Mann-Whitney U” and the “t student test”, depending of the variable to be analyzed. The Spearman test was used to correlate the variables, assuming 0.05 as a standard of significance between groups of patients.

RESULTS:

The table 1 shows the average scores and the standard deviation in both groups of patients and controls. The children with ALL presented higher scores using the CDRS-R when compared with controls and the difference was statistically significant (U=192.0; p<0.05). No significant difference was found between the two groups when using the CDI (U=474.0; p=n.s.).

TABLE 1

MEAN AND STANDARD DEVIATION BETWEEN THE ANALISED VARIABLES IN BOTH GROUPS.

VARIABLE	GROUP WITHLLA (N=31)		CONTROL GROUP (N=31)		
	MEAN	DP	MEAN	DP	U
AGE	9,55	2,39	9,55	2,39	510,5
CDI	8,8	4,2	9,6	4,8	474,0
CDRS	31,4	9,7	22,4	3,7	192,0*
TD	6,1	5,2	—	—	
TI	9,1	9,1	—	—	
HOSP	4,9	3,3	—	—	

TD = TIME WITH DIAGNOSIS - ALL (MONTHS)

TI = MEAN TIME OF PREVIOUS INTERNMENTS (DAYS)

HOSP = NUMBER OF PREVIOUS HOSPITALIZATIONS

*p = .000

The results of patients and controls evaluated by the CDRS-R and CDI are displayed at the Tables 2, 3, 4 and 5, highlighting the number of children with depressive symptoms. Seven children (22.6%) with ALL presented scores equal or higher than 40 (The cut-off for this scale previously defined

in the Brazilian population) and only one subject of the control group(3.2%) presented a score equal or higher than 40. Curiously, one child(3.2%) with ALL reached the cut-off of the CDI(≥ 18) and three subjects (9.6%) from the control group reached the cut-off for this scale.

TABLE 2
FREQUENCY AND PERCENT OF CDI
ALL GROUP

SCORES	N	%
1	1	3.2
2	1	3.2
3	3	9.7
5	1	3.2
6	2	6.5
7	1	3.2
8	5	16.1
9	4	12.9
10	4	12.9
11	4	12.9
12	1	3.2
13	1	3.2
14	1	3.2
16	1	3.2
22	1	3.2

OBS: In bold, frequency and percent of the child with score ≥ 18 .

TABLE 3
FREQUENCY AND PERCENT OF CDI SCORES
CONTROL GROUP

SCORES	N	%
2	1	3.2
3	2	6.5
4	2	6.5
5	2	6.5
6	2	6.5
7	3	9.7
8	2	6.5
9	2	6.5
10	2	6.5
11	3	9.7
12	4	12.9
13	1	3.2
14	1	3.2
15	1	3.2
19	1	3.2
21	1	3.2
22	1	3.2

OBS: In bold, frequency and percent of children with score ≥ 18 .

TABLE 4
FREQUENCY AND PERCENT OF CDRS-R
ALL GROUP

SCORES	N	%
20	3	9.7
21	1	3.2
22	1	3.2
23	2	6.5
24	2	6.5
25	2	6.5
26	2	6.5
28	1	3.2
29	2	6.5
30	1	3.2
31	2	6.5
33	1	3.2
34	1	3.2
35	2	6.5
36	1	3.2
41	1	3.2
42	3	9.7
50	1	3.2
55	2	6.5

Obs: In bold, frequency and percent of children with score ≥ 40 .

TABLE 5
FREQUENCY AND PERCENT OF CDRS-R
AT THE CONTROL GROUP

SCORES	N	%
17	2	6.5
18	5	16.1
19	1	3.2
20	2	6.5
21	1	3.2
22	6	19.4
23	4	12.9
24	1	3.2
25	3	9.7
26	3	9.7
29	1	3.2
41	1	3.2

OBS: In bold, frequency and percent of the child with score ≥ 40 .

Comparing each item of the CDRS-R between the groups of patients and controls we found no significant differences regarding the items: 5(appetite), 6(excessive fatigue), 7(physical complaint), 9(guilt), 12(morbid ideation), 17 (hypoactivity) (See table 6). Most of these items(except items 9 and 12) are part of somatic

symptoms of the CDRS-R. The item 19 of the CDI was the only one that showed statistically significant difference when comparing patients with controls($t=1.82$, $p=0.003$). The ALL group presented an average score of 1.03 (SD=0.91) and the control group an average score of 0.64 (DP=0.75).

TABLE 6

COMPARISON BETWEEN ALLGROUP AND CONTROL GROUP ACCORDING TO CDRS-R (The terms used at the Portuguese version were maintained to illustrate the terms used by the authors in Brazil)

CDRS-R ITENS	ALL		CONTROL		t	P
	MEDIA	SD	MÉDIA	SD		
1.TRABALHO ESCOLAR	1,64	0,83	2,09	1,04	-1.88	0.03
2.CAPACIDADE DIVERTIR-SE	1,96	1,64	1,06	0,35	2.99	0.002
3.REPRESSÃO SOCIAL	1,80	0,98	1,29	0,69	2.39	0.01
4.SONO	1,77	1,17	1,19	0,54	2.50	0.007
5.APETITE	1,74	1,06	1,35	0,91	1,54	0.65*
6.FADIGA EXCESSIVA	1,90	1,04	1,64	0,87	1.05	0.15*
7.QUEIXAS FÍSICAS	2,06	1,12	1,90	1,32	0.52	0.30*
8.IRRITABILIDADE	2,93	1,63	1,90	1,19	2.84	0.003
9.CULPA	1,25	0,51	1,12	0,34	1.16	0.25*
10.AMOR PRÓPRIO	1,74	0,96	1,25	0,81	2.13	0.02
11.SENTIMENTOS DEPRIMIDOS	2,51	1,45	1,09	0,79	4.77	0.000
12.IDEAÇÃO MÓRBIDA	1,67	0,87	1,93	1,93	-0.68	0.12*
13.ATOS SUICIDAS	1,19	0,54	0,90	0,30	2.61	0.006
14.CHORO	2,38	1,38	1,25	0,68	4.08	0.000
15.AFETO DEPRIMIDO	1,83	0,86	1,38	0,55	2.45	0.008
16.TEMPO DE LINGUAGEM	1,41	0,67	1,09	0,30	2.44	0.009
17.HIPOATIVIDADE	1,80	1,01	1,48	0,81	1.38	0.86*

* p=N.S

The ALL group presented a statistically significant correlation coefficient ($r_s=0.46$, $p<0.004$) between the CDI and CDRS-R scores, with a correlation index presenting a relatively low value. The control group presented a statistically significant correlation coefficient ($r_s=0.60$, $p<0.001$) between the CDI and CDRS-R scores, with a correlation index presenting a significant value when compared with the ALL group.

Correlation between the depressive symptomatology and the disease duration, after being diagnosed with ALL.

For these two variables we found a statistically significant inverse correlation between the scores of CDRS-R and the time passed after the diagnose of ALL ($r_s= -.43$; $p< 0.007$). There was no statistically significant correlation regarding this variable and the CDI ($r_s=-20$; $p=n.s.$).

DISCUSSION:

Previous analysis using the CDI to evaluate depressive symptomatology show average scores usually lower or similar compared to a control population of children, resembling our results^{5,6,17-19}. Some authors suggested different cognitive mechanisms underlying this finding and some of this hypothesis might be useful to explain the low scores for CDI in Brazilian children with ALL^{4,8,17}.

Canning et al (1992) used a specific algorithm to study the relation between cognitive styles of adaptation, characterized by repression, and depressive symptomatology that would explain the low scores obtained when using CDI. They studied thirty-one children, with various types of cancer (ALL, Sarcoma, etc) and 83 controls recruited from a public school. This study found a result similar to our, showing that the scores of the patients were lower compared to the control group, but the difference was not statistically significant. However, we did not infer any cognitive phenomenon that could explain our findings.

A similar approach was used by Phipps et al (1999) also studying a population of children with

cancer. They suggest that a style of repressive adaptation could be responsible for low scores of depressive symptomatology in several studies using self-assessment instruments^{4, 8, 11}. They concluded that: 1) These children are usually in a high risk for emotional stress due to various circumstances of disease and treatment. 2) The CDI format, and similar instruments, would allow a bias toward a minimization of the stress, reinforcing the "style of repressive adaptation".

The CDRS-R can overcome this last problem because it also inquires the parents or tutors about the child, differently than a self-assessment scale, and presenting a strong correlation with the DSM and the clinical diagnosis.

Our results displayed a higher frequency of depressive symptoms (presenting scores equal or higher than the cut-off) when we used the CDRS-R in patients with ALL compared to controls (22.6% vs 3.2%). Curiously, the somatic and vegetative symptoms did not present an important influence regarding the general sensibility of the CDRS-R when compared to the control group. The analysis with the CDI did not show significant differences.

Heiligenstein et al (1988) studied the role of somatic items in the CDRS-R under the diagnosis of depression in 24 children with cancer (average age of 12,25), eleven of them with ALL. They built a sub-scale of the CDRS-R, subtracting the items responsible for the somatic symptoms (appetite, sleep, fatigue, physical complaints, psychomotor slowing) and concluded that the sensibility for this instrument was not compromised. This result is similar to our findings.

We also noticed a correlation between the CDI and CDRS-R in the group of children with ALL, with a correlation index with weak significance, suggesting a possible cognitive influence (explained by the mechanisms previously mentioned) biasing the CDI toward low scores of depressive symptoms.

The correlation index between the CDI and CDRS-R in the control group presented a much higher significant value. This result coincides with other studies in the general population. Most of the

epidemiological studies about pediatric depression used the CDI as a screening test and found an important correlation with the CDRS-R, reinforcing the possibility of a cognitive mechanism typical of children with ALL, regarding self-assessment questionnaires (especially the CDI). Thus we see that it is necessary to use simultaneously more than one clinical tool, adding direct interview and clinical observation, in order to overcome the limits of self-assessment scales in children with cancer.

Another important finding is the inverse correlation between depressive symptomatology and the time passed after the diagnosis of ALL found by CDRS-R. This suggests that shortly after being diagnosed with ALL the children might experience important levels of emotional stress, displayed by more intense depressive symptoms, that might reflect in longer periods of hospitalization, chemotherapy and other more invasive medical procedures^{2,3,22}.

The early identification of depression in this particular pediatric population is important for both patients and mental health professionals, in order to provide a more efficient treatment, to increase rates and periods of surviving and even to plan ahead strategies of prevention.

Other important issue for future research in this field is to design longitudinal studies for patients with ALL in different steps of treatment, evaluating also the influence of family structure, personality traits, specific life events and the response to psychiatric and psychosocial interventions.

CONCLUSION:

- 1) The group of patients studied presented more intense depressive symptoms than the control group.
- 2) We found a higher frequency of depressive symptomatology when using the CDRS-R.
- 3) There was a discrepancy of findings when we compared a semi-structured questionnaire (CDRS-R) with a self-assessment scale (CDI).

- 4) There was an inverse correlation between depressive symptomatology and the time passed after the diagnosis of ALL found by CDRS-R.
- 5) In order to do a more efficiently diagnose depression in ALL patients it is necessary to routinely include clinical interviews with different approaches, both structured and semi-structured. A self-assessment scale, such as CDI, seems to be insufficient for this purpose.

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