

Approach to prediagnostic clinical semiology, noticed by mothers, of childhood acute lymphoblastic leukemia

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ABSTRACT

Introduction. Recognizing early symptoms of acute lymphoblastic leukemia (ALL) may help to make an early diagnosis. The objective of this study is to identify clinical manifestations preceding the diagnosis of childhood ALL from the maternal perspective and to establish the time elapsed from the first manifestation to the diagnosis.

Methods. Case study. Six hospitals located in Bogotá and Bucaramanga (Colombia) participated. Cases consisted of children under 15 years old with incidental diagnosis of ALL between January 2000 and March 2005. Data on sociodemographic characteristics, pre diagnostic clinical manifestations, first symptom, and time to diagnosis were collected during interviews with mothers. Medians, ranges and proportions were estimated. *P* values below 0.05 were considered significant.

Results. One hundred and twenty-eight cases were analyzed. Pallor (83.6%), loss of appetite (72.6%), weight loss (62.5%), and bleeding into the skin (39.1%) were the most common symptoms preceding diagnosis. The delay between the occurrence of the first symptom and the diagnosis of ALL depends on what the first manifestation is, and it may be shorter when there is evidence of hemorrhage (median= 14 days). The presence of palpable lymph nodes in the armpits was more significant in girls than in boys (*p*= 0.04).

Conclusion. Childhood ALL symptomatology in the prediagnostic stage is not specific to this disease; however, the clinical sign and time since its occurrence may serve as a guide in the early stage of this disease.

Key words: lymphoblastic leukemia, signs and symptoms, pediatrics, Colombia.

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INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common malignancy among children under 15 years old.^{1,2} Although certain medical treatments may achieve a five-year survival rate over 80%,³⁻⁶ it is also true that non-industrialized countries have difficulties to reduce ALL mortality and, as is the case of Colombia, mortality rates of childhood leukemias are higher there

than in other countries in the region.¹

Studies attempting to find etiological factors of ALL have been inconsistent, making it impossible to design strategies focused on reducing the risk of disease. A delay in the diagnosis and treatment initiation may contribute to a worsening in the prognosis and, consequently, a reduced long-term survival.^{9,10} One of the factors that may have a negative effect on the opportunity to make a diagnosis, and that can be potentially modified, is the lack of awareness of clinical signs and symptoms preceding the diagnosis of the disease both among family members and healthcare professionals. Although symptoms are not disease-specific if considered separately, when considered as a cluster they may serve better as a guide.^{11,12}

The objectives of this study were to identify the signs and symptoms preceding the diagnosis of childhood ALL from the perspective of mothers' experience and their manifestation patterns, and to establish the delay since the first clinical manifestation was observed to the time of diagnosis.

METHODS

History and criteria: This was a descriptive study based only on a group of cases selected in advance from a case-control study (primary study) targeted at establishing risk factors for ALL.^{13,14} In short, a case was defined as a child under 15 years old with an incidental histopathological diagnosis of ALL attending any of the six participating hospitals located in Bogotá and Bucaramanga (Colombia) between January 2000 and March 2005. Cases were identified by

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reviewing cancer institutes' databases or treating physicians' records. Adopted children or those having a family history of a first-degree relative with leukemia, Down's syndrome, a second primary tumor, or not living with their biological mother were excluded.

Collection of variables of interest

Data were collected using a structured questionnaire administered to mothers of selected children. A group of professionals outside the field of medicine was trained through educational workshops using a training system developed by the authors; these people were blinded to the study objectives, hypothesis and methodological aspects that were not necessary to their role. Mothers were interviewed personally to collect data on their child's demographic characteristics and clinical manifestations preceding the diagnosis of ALL. A special section of the original general questionnaire (primary study) was used to query about basic demographic characteristics and clinical manifestations preceding the diagnosis of ALL. Demographic characteristics of interest were parents' age at the time of birth, child's sex, age at diagnosis, socioeconomic level, and place of residence (urban or rural area). In addition, queried clinical signs and symptoms included pallor, vomiting, hematemesis, dizziness, loss of appetite, weight loss, epistaxis, enlarged lymph nodes in different body areas, bruises, petechiae, gingival bleeding, and blood in stools and urine. Additionally, an open question at the end of the questionnaire allowed mothers to report any other clinical manifestation observed prior to the diagnosis. Since it may be difficult to tell the difference between joint pain and bone pain, especially when a third party (in this case, the mother) is interviewed, these terms were grouped under the same category, which includes difficulty walking or getting up, bone pain or pain in the knee, elbow, arm, hip, back or leg. This manifestation was mentioned by interviewed mothers when answering the open question.

The first symptom was identified, and the time since its occurrence to the date of diagnosis (delay in diagnosis) was estimated as the difference in days between the date of diagnosis of ALL (recorded in the histopathological diagnosis form) and the date in which the mother recalled the occurrence of the first symptom. In order to confirm such date or to avoid missing values due to poor recalling, an additional question was specifically focused on the number of months or days elapsed until diagnosis.

Sample size

The number of cases included in this study was based on the total number of patients with ALL selected in the primary study; such sample size was estimated as per Schlesselman's criteria.¹⁵

Data entry and verification

Two Microsoft Access databases were created separately by trained people who were unaware of the study objectives. A visual verification was performed on the complete information included in the first database; errors and doubts were reviewed in survey form and corrected. A second database was prepared using the same information; these data were compared to the initial database and inconsistencies were verified and corrected.

Statistical analysis

Proportions were estimated for qualitative variables, and means or medians with their respective measures of dispersion for quantitative variables, as per the result of the Shapiro-Wilk's test for normality. The difference between two proportions of unpaired data was assessed using the χ^2 test. The difference between two mean values of unpaired data was estimated using Student's *t* test; if variables showed an abnormal distribution, non-parametric comparisons were performed using the Wilcoxon test for unpaired data. A *p* value of ≤ 0.05 was considered statistically significant. The statistical software used was Stata SE/11.0.

Ethical aspects

This study is based on an analytical study submitted before and approved by the Ethics and Scientific Committees of the following institutions: School of Health of Universidad Industrial de Santander (Bucaramanga, Colombia), COLCIENCIAS (Bogotá, Colombia), Terry Fox Run (Bogotá, Colombia), and participating hospitals and clinics. There were no risks for participants. Mothers participating in the study signed an informed consent form.

RESULTS

Participation flowchart

Out of 160 eligible cases from the primary study, 13 (8.1%) met an exclusion criterion. Out of all cases that had not been excluded (*n*= 147), 12 (8.2%) were not included because their parents refused to participate. Of the remaining 135 cases, in 7 (5.2%) mothers did not complete the survey on symptoms preceding the diagnosis. The

median time between the date of diagnosis and the date of the interview with the mother was 26.4 months (interquartile range [IQR]: 13.5-43.2), with cutoff values of 0.2 and 60.4 months.

General study data

A total of 128 children with ALL were included, 66 (51.6%) were male, and 54 (42.2%) were 1-4 years old at the time of diagnosis (Table 1). No differences were observed in terms of age at the time of diagnosis by sex (exact $p=1.0$).

Prevalence of prediagnostic clinical manifestations

The most common ALL clinical signs and symptoms included pallor (83.6%), loss of appetite (72.6%), weight loss (62.5%), bleeding into the skin (39.1%) (referred as petechiae, bruises and hematomas), dizziness or frequent falls (30.5%), and joint pain (28.9%). Blood in stools ($n=2$, 1.6%), hematuria ($n=3$, 2.3%), "hepatitis" (possibly jaundice or yellowing of the skin) ($n=1$, 0.8%), and varicella ($n=1$, 0.8%) were also included in the clinical manifestations reported by mothers as initial manifestations preceding the diagnosis.

The presence of lymph nodes in the armpits was more common in girls than in boys; this was the only statistically significant difference by sex ($p=0.049$). However, the percent comparison of "fatigue and tiredness" by sex showed a p value close to the significance value (Table 2).

It is worth noting that if lymph nodes in any body area were considered as a cluster, like the evidence of any bleeding, they would stand out among the most commonly observed signs preceding diagnosis.

TABLE 1. Distribution of acute lymphoblastic leukemia in children under 15 years old by sex and age

Age group	Sex		Sex		Total	
	Female	Male	Female	Male	Frequency	%
< 1	2	2	3.2	3.0	4	3.1
1-4	26	28	41.9	42.4	54	42.2
5-9	20	22	32.3	33.3	42	32.8
10-14	14	14	22.6	21.2	28	21.9
Total	62	66	100.0	100.0	128	100.0

First clinical manifestation and time to diagnosis

The most common clinical signs and symptoms referred as the first clinical manifestation preceding diagnosis do not necessarily follow the order of frequency indicated above. Pallor, fever, joint pain and bleeding into the skin were more commonly described as the first sign or symptom (Table 3).

A total of 109 (85.2%) mothers recalled the time from the first clinical manifestation to diagnosis of ALL in their children. The median number of days between these two events was 30 (IQR: 15-90). There were no differences in the median number of days since the occurrence of the first symptom until diagnosis by sex ($p=0.86$),

TABLE 2. Frequency of clinical manifestations reported by mothers as preceding the diagnosis of acute lymphoblastic leukemia in their children

Sign/symptom preceding the diagnosis ¹	Female sex		Male sex		Total	
	n	%	n	%	n	%
Pallor	54	87.1	53	80.3	107	83.6
Hyporexia/anorexia	46	74.2	47	71.2	93	72.6
Weight loss	36	58.1	44	66.7	80	62.5
Bleeding into the skin	28	45.2	22	33.3	50	39.1
Dizziness/falls	21	33.9	18	27.3	39	30.5
Joint pain	18	29.0	19	28.8	37	28.9
Fever	19	30.7	16	24.4	35	27.3
Lymph nodes in the neck	18	29.0	17	25.8	35	27.3
Nosebleed	16	25.8	17	25.8	33	25.8
Vomiting	15	24.2	13	19.7	28	21.9
Fatigue, tiredness ²	10	16.3	19	28.8	29	22.7
Gingival bleeding	11	17.7	7	10.6	18	14.1
Recurrent influenza	8	12.9	3	4.6	11	8.6
Lymph nodes in the armpits	8	12.9	2	3.0	10	7.8
Coughing up blood	7	11.3	5	7.6	12	9.4
LNGLL	6	9.7	4	6.1	10	7.8
NSAS	6	9.7	4	6.1	10	7.8
Headache	1	1.6	4	6.1	5	3.9
Vomiting blood	2	3.2	2	3.0	4	3.1

¹ The most common name reported by the mothers was used, or if they were similar, signs were grouped under a common name.

² $p=0.08$ for "fatigue and tiredness" when comparing the frequency of symptoms by sex.

LNGLL: lymph nodes in the groin or lower limbs.

NSAS: non-specific and rare abdominal signs and symptoms (diarrhea, stomachache, abdominal pain, inflammation of the stomach).

place of residence in a rural area ($p=0.58$), or socioeconomic level ($p=0.92$). In each comparison category, the median time was 30 days. There was also no statistically significant difference observed when considering the number of reported symptoms (cluster of 3 or less symptoms: median of 30 days, cluster of 3 or more symptoms: median of 30 days; p value: 0.635).

Patterns (combinations) of most common clinical manifestations

The number of clinical signs or symptoms preceding diagnosis ranged from 1 to 12; however, the most common cluster included 4-5 signs or symptoms (Figure 1). Regardless of the total number of manifestations preceding the diagnosis in each patient, the most common pairs of signs and symptoms included pallor and loss of appetite ($n=83$, 64.8%), loss of appetite and weight loss ($n=72$, 56.2%), pallor and weight loss ($n=71$, 55.5%), pallor and bleeding into the skin ($n=45$, 35.2%), pallor and dizziness ($n=33$, 25.8%), pallor and arthralgia ($n=32$, 25.0%), pallor and lymph nodes in the neck ($n=32$, 25.0%). In addition, the most common trios of symptoms were pallor, loss of appetite and weight loss ($n=65$, 50.8%), pallor, loss of appetite and bleeding into the skin ($n=35$, 27.3%), and dizziness, loss of appetite and weight loss ($n=29$, 22.6%). Considering only those children who

experienced arthralgia preceding the diagnosis, the most commonly associated symptoms included pallor ($n=32$, 86.5%), loss of appetite ($n=26$, 70.3%), weight loss ($n=23$, 62.2%), and bleeding into the skin ($n=14$, 37.8%).

When analyzing the delay since the occurrence of the first sign or symptom to the diagnosis of ALL, it is observed that the median time was 40 days (i.e., 50% of children were diagnosed at 40 days or earlier) when pallor was the first manifestation, 30 days with arthralgia, 25 days with fever, and 14 days with any form of bleeding into the skin.

DISCUSSION

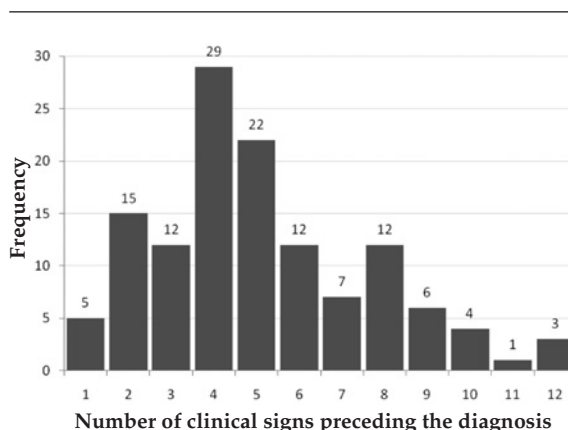
There is still interest regarding the clinical signs and symptoms preceding the diagnosis of childhood cancer, and a review of certain publications on this topic shows that the findings of this study are comparable.^{11,12} ALL most commonly occurs at 3-4 years old, and this is similar to the distribution of cases in this research.^{16,17} One of the strengths of this study is that data were obtained directly from the mothers of children with ALL, therefore reducing the risk of an incorrect classification, unlike studies using medical records as source of data, whose original purpose is not to be used in research. There might be a bias in the classification of prevalence of clinical manifestations preceding diagnosis due to the differences in the time between the diagnosis of ALL and the interview with the mother. In this sense, an exercise (not shown before) aimed at establishing possible changes in the prevalence of the same symptom by time quartile between these two events (diagnosis and interview)

TABLE 3. First clinical manifestation preceding the diagnosis as reported by the mother

Reported manifestation	Frequency	%	% Accrued
Pallor	50	39.1	39.1
Fever	19	14.8	53.9
Joint pain	15	11.7	65.6
Bleeding into the skin	9	7.0	72.7
Nosebleed	6	4.7	77.3
Lymph nodes in the neck	6	4.7	82.0
Stopped eating	4	3.1	85.2
LNGLL	4	3.1	88.3
Weight loss	4	3.1	91.4
Fatigue - tiredness	3	2.3	93.8
Recurrent influenza	3	2.3	96.1
Vomiting	3	2.3	98.4
Hepatitis	1	0.8	99.2
Dizziness/falls	1	0.8	100.0

LNGLL: lymph nodes in the groin or lower limbs.

FIGURE 1. Number of clinical manifestations observed by mothers preceding the diagnosis of acute lymphoblastic leukemia on their children



found no statistically significant differences when assessing the proportions reported for pallor, dizziness, weight loss, and vomiting blood. However, loss of appetite (hyporexia/anorexia) was perceived differently depending on the time elapsed; however, unlike what was expected, this manifestation was most commonly reported by mothers interviewed much time after the diagnosis (longest quartile). Although a differential recall based on time cannot be ruled out in this case because such specific symptom is easily remembered and is remarkable once it occurs, it is possible that these proportions differ from what actually occurred. In addition, the form allowed mothers to describe other symptoms not included in the survey, which improved knowledge on clinical manifestations and their occurrence patterns before children are diagnosed. Joint/bone pain was not included in a specific question, so it is possible that the prevalence reported here is lower than the actual prevalence (these symptoms were reported under the open question: "Did your child have other symptoms? Please describe them.").

Although pallor, bleeding manifestations and non-specific body symptoms tend to be part of the most common cluster of signs and symptoms, as mentioned in the scientific literature,^{11,18} it should be underscored the high proportion of patients who could have joint or bone pain, which may lead to a misdiagnosis. Unawareness of warning signs and symptoms or a symptomatic initial management may eventually hinder a better treatment response, although more than 70% of patients may finally be cured.^{4,6} Joint symptoms and their potential for confusion with other diagnosis have been the focus of some studies.^{19,22} Among such studies, the one conducted by Jones established that, in children with unexplained musculoskeletal manifestations, the three most common findings that predicted the diagnosis of ALL were a low leukocyte count, a normal-low platelet count, and a history of night pain; when these three were present, there was a 100% sensitivity and an 85% specificity.²² The presence of significant lymphadenopathy should increase the suspicion of childhood leukemia.¹¹ In our research, mothers usually reported this sign in their children, with a difference in its prevalence by sex. Notwithstanding this, authors did not find a similar comparison in the reviewed literature.

In this study, it was not possible to establish a difference in the time from symptom initiation to the date of diagnosis by sex, socioeconomic level or place of residence in a rural area. However,

it should be noted that the municipalities from where cases came from corresponded to departmental capitals or other municipalities close to the participating institutions; therefore, areas with transport problems or higher poverty indices may have varying results. Similarly, there was no variation in time depending on the number of reported symptoms, but rather, there might be in relation to the type of manifestation. It should be taken into account that such period is actually made up of two different periods: time from the first symptom until the mother makes a consultation with the healthcare team for the first time, and time since this first consultation to the definite diagnosis. The interim date (first consultation on symptoms with the healthcare team) was not queried.

Therefore, the time elapsed since the first clinical manifestation to the diagnosis of ALL may depend on the clinical sign perceived by the mother and possibly on the subjective clinical seriousness assigned by the mother or the healthcare team during the first consultation. Short-term clinical signs, immaturity of affected cells, and a high leukocyte count have been described as helpful to establish the diagnosis of acute leukemia.²²

To sum up, the results of this study are consistent with the literature. Among all clinical manifestations preceding diagnosis reported by mothers, the prevalence of joint pain is striking since this was described in an open (not direct) question at the end of the survey. Knowing the most common symptoms, the first clinical manifestation of ALL and its occurrence patterns at the time of consultation is a first step to establish the characteristics of ALL among Colombian children, and may help to warn families and physicians so as to make an early diagnosis and provide an equal access to healthcare. ■

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