



RESEARCH ARTICLE

Signs, Symptoms and Findings in Complete Blood Cell Count at Diagnosis in Children with Acute Leukemia

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Abstract

Introduction: Acute leukemias are the most frequent malignancy in children, some of their clinical manifestations are not considered in the first medical evaluations, making a prompt diagnosis a challenge.

Purpose: The aim of this study is to describe signs and symptoms and characteristics of the first complete blood count at diagnosis of children with acute leukemia.

Methods: Cross sectional study, a total of 543 children, 456 with acute lymphoid leukemia and 87 with acute myeloid leukemia under 18 years of age and diagnosed at a pediatric cancer center in Bogota, Colombia between 2007 and 2016. Clinical records were systematically reviewed for the main complaint, history of present illness, physical examination findings at the first medical evaluation and data from the first complete blood count.

Results: Median age for patients was 6 years. Most frequent clinical findings were pallor and fever followed by asthenia, adynamia, lymphadenopathy and haemorrhagic manifestations. Blood cell count was abnormal in all patients with acute myeloid leukemia and 98% of acute lymphoid leukemia patients.

Conclusions: The initial symptoms of acute leukemia are nonspecific. It is important for physicians to become aware when to suspect cancer in children and conduct a complete evaluation when the possibility of this diagnosis exists, in order to an early referral for diagnostic confirmation.

Keywords: Acute lymphoblastic leukemia; Acute myeloid leukemia; Clinical manifestations; Signs and symptoms; Complete blood count

Abbreviations: ALL: Acute Lymphoblastic Leukemia, AML: Acute Myeloid Leukemia, CBC: Complete blood count, WBC: White Blood Count, HOMI: Fundación Hospital de la Misericordia

Introduction

Cancer in children is a rare disease, accounting for 0, 5-3% of all neoplasms, and is the second leading cause of death in children in developed countries [1]. Acute leukemias are the most common cause of childhood cancer [2]. By 2016 in the United States, 18 of every 100,000 children under 19 years had some type of cancer; 52% attributed to acute leukemia in children under 14 years of age [3]. The initial symptoms of childhood leukemia are usually non-specific and difficult to distinguish from those that characterize self-limited illnesses, and can be attributed to frequent childhood illnesses [4]. Despite the fact that survival rates for acute leukemia have improved to 85% - 90% at 5 years [5], there are still being some barriers in the diagnosis that probably limit patients achieving better survival rates, mainly in developing countries [4].

For physicians working in primary care, it is not easy to get a diagnosis due to the low frequency of this disease, thus a high index of suspicion is required to identify patients promptly. Bernbeck et al. [6] conducted an observation study at the Clinic for Pediatric Oncology of the University Hospital in Duesseldorf, Germany, where at least 75% of children had a short medical history of several weeks and had unspecific clinical symptoms, enlarged lymph nodes, hepatomegaly and/or splenomegaly. A complete blood count (CBC) was sufficient since all presented with abnormalities [6]. Nevertheless, a limitation in the approach of this topic is present. Despite the fact that in recent years the diagnosis of leukemia has increased, it is still being rare in children, and therefore, studies including initial signs and symptoms at diagnosis are very scarce. Clarke et al. [7] conducted a meta-analysis in which 33 studies from 21 countries were included, that study describes the signs and

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Received: June 15, 2018; **Accepted:** June 18, 2018; **Published:** June 20, 2018

symptoms of cancer at diagnosis [7]. This study is the largest reference in recent literature embracing 3084 children and adolescents.

In Colombia during 2015, 923 new cases of cancer in patients younger than 18 years old were reported, with a prevalence of 274 cases per 1million children and an incidence of 54/1.000.000. Acute lymphoblastic leukemia accounted for a 60% of all cases and acute myelogenous leukemia 5% of all types of cancer [8, 9]. The aim of this study is to describe the signs and symptoms at diagnosis and characteristics of the first complete blood count of patients with Acute Lymphoblastic Leukemia (ALL) and Acute Myeloid Leukemia (AML) diagnosed between 2007-2016 at Fundacion HOMI Hospital de La Misericordia, a pediatric cancer reference center in Bogotá, Colombia.

Methods

Descriptive cohort observational study in patients under 18years of age with a confirmed diagnosis of acute leukemia, Fundación HOMI Hospital La Misericordia Bogota, Colombia from January 2007 to December 2016. A review of medical history records was held. Data came from the cohort of 3 treatment protocols for acute leukemia between 2007 and 2016. Records were reviewed for the main complaint, history of present illness, physical examination findings at the first pediatric medical evaluation and data from the first complete blood count (CBC). The data were double checked to assure their validity.

Thrombocytopenia was defined as a platelet count of 100×10^9 /mL or below. For anaemia age was taken into account and values changed as follow: for patients aged 0-1 year anemia was haemoglobin levels below 10gr/dL, for 1-2 years of age haemoglobin below 11gr/dL and patients 3years and older levels below 12gr/dL. Leukocytosis was defined as a white blood cell count above 20×10^6 /mL, hyperleukocytosis above 100×10^6 /mL and leukopenia below 4×10^6 /mL. A descriptive analysis of the information was done. The qualitative variables presented with absolute and relative frequencies, the quantitative variables with measures of central tendency and dispersion according to the distribution of the data. The ethics committee of the institution approved each of analyses according to treatment protocol (approval dates January 20, 2015, October 5, 2015 and July 15, 2016).

Results

543 patients were included, 456 (83,9%) with ALL and 87 (16%) with AML. The median age was 6 years (IQR 3 -11), for children with ALL 6 years (IQR 3-11) minimum 0.6 year, maximum 18 years and for AML 8 years (IQR 3-12) minimum 0.1 year and maximum age 17 years. For both types of leukemias, the most frequent manifestations were pallor and fever, followed by asthenia, adynamia, lymphadenopathy and haemorrhagic manifestations. Table 1 shows the clinical manifestations and their frequencies according to type of acute leukemia. All patients had at least 3 associated symptoms in the consultation motif. There is a greater proportion of mucosal

bleeding in patients with AML, besides gingival hemorrhage and epistaxis, more than twice as much compared to ALL, as well as hemorrhagic manifestations in the skin (hematomas and petechiae) with 41 vs. 171. Osteoarticular manifestations were more frequent in patients with ALL than in AML, 28.8% vs 15 %. Gastrointestinal manifestations such as diarrhea, abdominal distention, hepatomegaly, hepatosplenomegaly was higher in AML than in ALL 55 vs 231.

The CBC was abnormal in all children with AML and near 98% of the children with ALL: anemia and thrombocytopenia were the most frequent findings. In 39% of all patients with ALL there was a normal white cell count. In table 2 there are the findings of the CBC. The median time of signs and symptoms before consultation was 20 days (IQR 8-30) minimum 0.5 maximum 365. For AML median was 30 days (IQR 9-30) minimum 1 maximum 360, and for ALL median was 20 days (IQR 8-30) minimum 0.5 maximum 365.

Discussion

The incidence of childhood cancer is between 100 and 150 cases per million among people under the age of 15, and the incidence for acute leukemia in children is between 35 and 50 cases per million in a population under the age of 15 [2]. There is little literature that describes the clinical manifestations of children with acute leukemia at diagnosis. One metaanalysis with 3084 patients [7], one from Iran [10], two studies from Latin America, Paredes et al. [11] from Mexico and Robazzi [12] from Brazil dedicated to this topic. This is the first study in Colombia that illustrates the initial signs, symptoms and blood cell count analysis and the differences among children with ALL and AML.

The most frequent manifestations in our study were pallor and fever with similar representation among both groups, fever 55,8 % pallor 53,7% these findings were similar to those in Clarke et al. [7], were fever was present in 53% and pallor 54%. Karimi et al. [10], conducted in Southern Iran a study with 275 children with acute leukemia the most common sign was fever 73% followed by pallor 43%. Other manifestations followed in frequency were asthenia, lymphadenopathy and bleeding; the last is the most frequent in AML (53% vs 37.5%). The most frequent site of bleeding was cutaneous (hematomas, petechial, echymosis) with 55% in AML and 30,2% in ALL; also for mucosal haemorrhage, it was more than double in AML (34,4% vs 5,4%), Karimi et al. [10] found a similar proportion for AML (32% vs 16%).

Osteoarticular manifestations can be present as an early manifestation in children with acute leukemia, some authors described symptoms in a 23 % [10], between 26% and 43% [7] and 54, 5% [12]. In all the studies it was more frequent in ALL than in AML. It is important to highlight that Robazzi et al. [12] had a higher proportion in osteomuscular manifestations, almost double than Karimi et al. [10] and slightly higher than ours, but this study was orientated specifically to these manifestations as initial signs of leukemia and have a better description of signs and symptoms compared to other studies.

Clinical Characteristics	AML n= 87	%	ALL n= 456	%	AML- + A n= 543LL	%
Fever	51	58,6	241	52,8	292	53,7
Asthenia, adynamia	35	40,2	191	41,9	226	41,6
Pallor	57	65,5	246	53,9	303	55,8
Joint pain	8	9,2	79	17,2	87	15,7
Muscular pain	9	10,3	21	4,6	30	5,4
Lymphadenopathy	38	43,7	167	36,6	205	37,5
Bleeding	46	52,9	166	36,4	212	39
Epistaxis	16	18,4	40	8,7	56	10,1
Ecchymosis and petechiae	41	47,1	171	37,5	212	39
Hematomas	7	8,0	7	1,5	14	2,5
Gingivorragia	11	12,6	24	5,2	35	6,3
Hematemesis hematoquezia	3	3,4	8	1,7	11	2,0
Anorexia /hyporexia	15	17,2	58	12,7	73	13,4
Vomiting	6	6,9	31	6,8	37	6,7
Jaundice	4	4,6	25	5,2	29	5,3
Odynophagia	5	5,7	14	3,0	19	3,4
Edemas	4	4,6	20	4,4	24	4,3
Hepatosplenomegaly	55	63	50	231	286	51.60%
Hepatomegaly	14	16,1	38	8,3	52	9,4
Splenomegaly	2	2,3	12	2,6	14	2,5
Headache	16	18,4	33	7,2	49	9,0
Respiratory symptoms	29	33,3	74	16,2	103	18,9
Bone Pain	6	6,9	59	12,9	65	11,9
Antalgic gait	2	2,3	33	7,2	35	6,4
Lumbar pain	1	1,1	27	5,9	28	5,15
Abdominal distension	5	5,7	11	2,4	16	2,9
Abdominal pain	13	14,9	69	15,1	82	15,1
Diarrhea	5	5,7	21	4,6	26	4,7
Weight loss	17	19,5	57	12,5	74	13,6
Soft tissue tenderness/Mass	4	4,6	12	2,6	16	2,9
Skin Lesions (Nodules, Rash, Erythema, Ulcers)	6	6,9	24	5,2	30	5,4
Time In Days Between The Onset Of Symptoms And Time To Consult to hospital (Median)	30		20			

Table 1: Clinical characteristics and frequency according to leukemia at diagnosis.

CBC Findings	AML n= 87	%	ALL n= 456	%	All leukemias n= 543	%
Anemia	77	88,5	406	89	483	88,9
Thrombocytopenia	66	75,8	359	78,7	425	78,2
Leucopenia	17	19,5	127	27,8	144	26,5
Leukocytosis	39	44,8	151	33,1	190	35
Hyperleukocytosis	8	9,2	36	7,8	44	8,1
Normal white blood cell count	31	35,6	178	39	209	38,5
Neutropenia	39	44,8	274	60	313	57,6
Blasts in peripheral blood	58	66,6	210	46	268	38,7
Normal CBC	0	0,0	10	2,2	10	1,8
Pancytopenia	8	9,2	97	21,3	105	19,3

Table 2: Count blood cells findings at diagnosis of patients with leukemia.

Gait abnormalities and bone pain was 2 -3 times more frequent in Robazzi et al. [12] study.

Visceromegaly is one of the signs that physicians most frequently seek to find in patients of acute leukemia, as a manifestation of malignant infiltration. We documented 51%

of hepatomegaly and splenomegaly being more frequent in patients with LMA (63% vs 50%). These results are similar to Clarke's [7] that was present in a 42%, with no differential analysis among leukemia subtypes. In Latin America since 1990 two previous studies were conducted characterizing childhood leukemia. Paredes-Aguilera et al. [11] studied 29 cases of

acute megakaryoblastic leukemia in children in Mexico City. The clinical symptoms included 96.6% progressive pallor, 69% irritability, fatigue, headache, hyporexia, 27.6% bone pain and 20.7% bleeding manifestations, and 96% presented with anemia. In our results pallor was seen in 65% in ALL and 52.9% in AML patients. Bleeding manifestations were higher and bone pain was present in a lesser extent. Robazzi et al. [12] reviewed 414 patients 77.1% with ALL and 22.9% with AML, osteoarticular manifestations were present on 54.7% of the patients with acute leukemia, with a higher frequency among patients between 1 and 9 years of age 58.7%.

In Colombia in 2005, 4.5% of deaths in children fewer than 15 years were due to cancer and 45% of these deaths were patients with leukemia [8]. In 2011, the Facts and Actions Bulletin related to mortality from pediatric leukemia in Colombia, the time between the first visit and the diagnosis was reported for up to 221 days [13] this finding maybe suggests a low suspicious level for this diagnosis, among other reasons. Uncommon signs and symptoms such as gum hypertrophy (7.9%) and proptosis (6.3%) was seen in AML cases.

We found that all patients with AML had an abnormal CBC; the main findings were anemia and thrombocytopenia. In patients with ALL, 2% of them had a normal CBC. For those with an abnormal examination, the most common findings were anemia, thrombocytopenia and neutropenia.

Blasts in the peripheral blood smear, were found in 43.3% of all the patients, and were a more frequent finding in patients with ALL. This is important to emphasize since most physicians would expect to find blasts in the CBC. Our results are similar to Robazzi's [12] who showed absence of blasts in 48.0% of the cases (ALL=53.5% and AML = 30.1%). Another finding, that is usually reviewed by health practitioners in patients with suspicious of leukemia, is the white blood count (WBC), it's important to mention that there were more normal WBC than abnormal counts in patients with ALL (45,6%), similar to results of Brazilian children and adolescents (12) who presented with 52.2% of normal WBC. Hyperleukocytosis is the less frequent finding, 4,6% for AML and 7,9% for ALL. In 331 patients with ALL and 61 with AML there were anemia and thrombocytopenia combined, this was the most frequently found bicytopenia.

Conclusion

It is important to educate physicians who work with pediatric population, to suspect cancer and recognize the signs of alarm suspect the disease, conduct a targeted evaluation and to identify when to refer to centres for diagnostic confirmation. With the characterization of the symptoms, signs and laboratory findings of patients with leukemia in our country,

we seek to provide a guide to promote understanding of the clinical presentation of this pathology and to help consider the diagnostic possibility in those physicians that take care of patients less than eighteen years.

Conflicts of Interest

The authors declared that there are no conflicts of interest.

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Citation: Rumilla MIV, Ballesteros AL, Cardozo MÁR, Tamara L, Urbina ICS, et al. (2018) Signs, Symptoms and Findings in Complete Blood Cell Count at Diagnosis in Children with Acute Leukemia. *Pediatr Res Child Health* 1: 001-004.

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