ORIGINAL ARTICLE

Received: February 2020
Accepted: April 2020

Common Presenting Signs and Symptoms in Children with Acute Lymphoblastic Leukemia

Ehsan Shahverdi[1], Mehdi Shahriari[2], Soonia Zare[2], Mohammad Saeid Rahiminejad[2], Fatemeh Hosseinpour Soleimani[3]*, Massoumeh Maki[4], Rojen Manouchehri[5], Mourad Haj Abdo[1]

ABSTRACT

Background: Acute lymphoblastic leukemia (ALL) is one of the blood cancers responsible for 80% of children's leukemia and is also the most common malignancy in patients aged under 14 years (frequency of 23% among all types of cancers). Regarding the importance of identifying clinical symptoms to diagnose the disease in the early stages, this study is conducted to investigate the symptoms at diagnosis in ALL children.

Methods: In this retrospective cohort study, 350 patients aged under 14, referring to four hospitals of Shiraz University of Medical Sciences as reference hospitals in Southern Iran, participated between 2013 and 2019. Their information was collected using patients' records, and the data were analyzed using SPSS version16.

Results: Based on the findings of this study, the first clinical manifestations of the disease happened suddenly and acute, occurring within a few days to a maximum of 6 weeks before diagnosis. Fever (70%) and hepatomegaly (60%) were the most common signs and symptoms in patients. However, a significant percentage of ALL patients referred with non-specific symptoms.

Conclusion: The results of this study indicate the importance of recognizing common and unusual signs and symptoms based on a complete and thorough history taking and accurate physical examination as well as rare symptoms that may be ignored or misdiagnosed by physicians. The knowledge of common signs and symptoms results in early diagnosis of the disease in early stages.

Keywords: Acute Lymphoblastic Leukemia; Symptom, Leukemia

1. Department of Cardiology and Angiology, Bonifatius Hospital Lingen, Academic Teaching Hospital of the Medical Faculty of the Westphalian Wilhelms University of Münster, Lingen, Germany.
2. Department of Pediatrics, Shiraz University of Medical Sciences, Shiraz, Iran.
3. Student Research Committee, Bushehr University of Medical Sciences, Bushehr, Iran.
4. Department of Nursing and Midwifery, Falavarjan Branch, Islamic Azad University, Isfahan, Iran.
5. School of Medicine, Tehran Medical Sciences Branch, Islamic Azad University, Tehran, Iran.

***Corresponding Authors:**
Fatemeh Hosseinpour Soleimani
Student Research Committee, Bushehr University of Medical Sciences, Moallem St, Bushehr, Iran
Tel/ Fax: (+98)773340089
Email: Fa.hosseinpour73@yahoo.com

BCCR
2020; 12(1):26-33
www.bccrjournal.com

INTRODUCTION:

Cancer is a leading cause of death worldwide, accounting for 8.8 million deaths in 2015. Approximately 1,688,780 new cancer cases and 600,920 deaths due to cancer were reported in the United States in 2017 (1). Leukemia, as one of the most common cancers in Iran with more than 30000 new cases reported annually, is a progressive and malignant disease of the hematopoietic cells caused by the proliferation and development of white blood cells (WBCs) and their precursors in the blood and bone marrow (2). Acute lymphoblastic leukemia (ALL) is one of the blood cancers that occurs in the precursor cells of the B or T lymphocytes. ALL is responsible for 80% of children's leukemia and is also the most common malignancy in patients aged under 15 years (with a frequency of 23% among all types of cancers) (3).

In ALL, the number of leukemic lymphoblasts increases, and the accumulation of these cells in the bone marrow prevents the normal development and function of the blood cells. Thus, the immune system cannot cope with the infections. Precursor B-cell ALL (PBC-ALL) is the most common form of ALL, especially in children aged 1-15 years. Hyper diploid cellular clones with t(12; 21) (p13; q22) and t(1.19) are the main cause of the disease (30%). Proleukemia cells in this disease require environmental stimuli to become completely cancerous. The environmental stimuli and the exact cause of ALL are not known. However, malignancy seems to occur as a result of the accumulation of mutations in genes. Studies have shown that duplication of der (21) t(12; 21) looks like trisomy 21 in rare cases (4,5). Certain environmental risk factors, such as high levels of radiation, certain chemicals, and human T-cell leukemia virus (HTLV-1), are associated with ALL. The role of infection as a strong stimulus in the progression of ALL has been known recently. Those with Trisomy 21 are also at risk of ALL (6-10).

Ineffective bone marrow cells, gingival bleeding, purple skin lesions, and small subcutaneous hemorrhages, pain, fever, Infections associated with cytopenia, anemia, thrombocytopenia, lymphadenopathies, hepatomegaly or splenomegaly, central nervous system disorders, testicular and skin infiltration, weakness and fatigue, abdominal discomfort (due to splenomegaly), lymphadenopathy especially in the neck or axillary, and weight loss are seen in this disorder (11, 12).

Finding early symptoms plays a key role in early diagnosis, and subtyping of acute leukemia leads to proper treatment, monitoring the efficacy of treatment, prognosis, and the identification of minimal residual disease (MRD). In this study, we evaluated the prevalence of clinical symptoms in children diagnosed with ALL aged under 14 in four Hospitals of Shiraz University of Medical Sciences.

METHODS:

In this retrospective cohort study, 350 patients aged under 14 referred to four hospitals of Shiraz University of Medical Sciences in 2013-2019 participated. After obtaining written informed consent, to determine the prevalence of clinical signs and symptoms at leukemia diagnosis, a list of patients admitted in these 4 hospitals was obtained. From a total of 396 cases (80 cases in Namazi Hospital, 145 cases in Hazrat-e- Ali Asghar Hospital, 126 cases in Shahid Faghihi Hospital, and 45 cases in Shahid Beheshti Hospital), 350 cases were finally studied. Others were excluded because of inadequate or duplicate information or referral due to relapse. Patients were classified into three age groups (under one year, between 1 to 10 years and 10 to 14 years). Symptoms were categorized into two groups: the sign (symptom received by the physician) and the symptom (symptoms pronounced by the patient).

The signs include fever, restlessness, pallor, petechiae, ecchymosis, edema (particularly around the eyes),

skin manifestations, nose bleeding, gingival bleeding, enlargement of the lymph nodes in the mediastinum, testicular enlargement, cerebral palsy, eczema on the abdomen, erythema on the face and hands, weight loss and cardiac murmurs. The symptoms include fever, lethargy, early fatigue, pallor, bleeding, rapid bruising, abdominal bloating, bone pain, joint pain, unbalanced walking, inability to walk, vomiting, headache, respiratory distress, skin rash, an abnormal penile and anorexia. Data were analyzed using statistical package for social sciences (SPSS) version 16 (SPSS Inc. Chicago, IL) for windows. Results were statistically analyzed using the Chi-square test, and a P value of less than 0.05 was considered significant.

RESULTS:

In this study, the medical records of patients containing the information needed to evaluate the prevalence of ALL clinical signs and symptoms at the time of the first referral to the physician were investigated. In this study, the male to female ratio was 1.3 (350 boys vs. 198 girls). Also, children in different age groups were studied. The age group of 1-10 years old, with 81.6% of the total children, was the most frequent. The group older than 10 years with 17.5% was the second, and the age group under one year with 0.9% was the least frequent.

Signs and symptoms:

In most of the patients under evaluation, the first clinical manifestations happened suddenly and acute occurring within a few days to a maximum of 6 weeks before the diagnosis. Thus, the onset of these manifestations rarely exceeded a few months. Generally, the signs and symptoms at diagnosis can be classified into two groups of specific and non-specific. A significant percentage of patients referred with non-specific signs and symptoms, such as weakness, anorexia, and weight loss. Specific signs and symptoms were observed including, bone marrow dysfunction that results in inadequate blood cells and various infections, and some other relatively common organ involvements consist of the central nervous system (CNS), urinary tract, gastrointestinal (GI) tract, respiratory tract, and skin.

Fever (70%) and hepatomegaly (60%) were the most common signs and symptoms in patients (**Table 1**). Fever was the most common clinical manifestation in ALL patients, which was associated with pallor (35%) and chills (11%).

Children with ALL are occasionally misdiagnosed with rheumatoid arthritis and treated with anti-inflammatory drugs. Approximately 23% of patients had bone pain, 14% had arthralgia, and 16% complained of weakness and early fatigue.

A significant percentage of ALL patients referred with non-specific symptoms. In the present study, there were many uncommon signs and symptoms with the prevalence of 0.02 - 0.002 (**Table 2**).

DISCUSSION:

This study was conducted to evaluate the prevalence of clinical symptoms at the time of diagnosis in ALL patients aged under 14 in four Hospitals of Shiraz medical university. Based on the findings of this study, in most people, the first clinical manifestations of the disease happened suddenly and acute occurring within a few days to a maximum of 6 weeks before the diagnosis. The most common signs and symptoms were fever (70%) and hepatomegaly (60%). According to a similar study, among the clinical symptoms of leukemia, fever was mentioned as the most common clinical symptom, with a prevalence of 60.7% (13). Thus, children with unspecified fever should not be missed.

Bone marrow defects, abnormal cellular metabolism, and infiltration of cancer cells in various organs result in wide-spread symptoms (11, 12). Defects in patients' bone marrow lead to signs of inadequate production of erythrocytes, platelets, and granulocytes. Ineffective erythropoiesis leads to symptoms of anemia, including shortness of breath, headache, feeling sick, tiredness,

Table 1. Common signs and symptoms at diagnosis in children with ALL, as number (n) and percentage (%)

Signs and symptoms	n	%
Fever	234	66.85
Pallor	182	52.00
Fever with Pallor	108	30.85
Fever with chills	37	10.57
Bone pain	80	22.85
joint's pain	47	13.42
Inability to walk	11	3.14
Anorexia	117	33.42
Weight Loss	81	23.14
productive cough	81	23.14
Weakness	65	18.57
Night sweats	38	10.58
Feeling unwell	11	3.14
Headache	56	16.00
Heart murmur	26	7.42
Vomiting	73	42.85
Nosebleed	49	14.00
Bleeding from the gums	22	6.28
Diarrhea	30	8.57
Cough	16	4.57
Throat redness	11	3.14
Ecchymosis	51	14.57
Petechiae	42	12.00
Large testicles	13	3.71
Abdominal pain	40	11.42
Constipated	28	8.00
Edema around the eyes	26	7.42
Mass in mandible	10	2.85
Diffuse Edema	10	2.85
Hepatomegaly	201	57.42
Enlargement of the lymph nodes (Lymphadenomegaly)	174	49.71
Splenomegaly	162	46.28

Table 2. Uncommon signs and symptoms at diagnosis in children with ALL, as number (n) and percentage (%)

Signs and symptoms	n	%	Signs and symptoms	n	%
Impaired balance	1	0.2	Retina bleeding	5	1.42
Flatulence	8	2.28	Hematemesis	4	1.14
Fatigue	8	2.28	Black stool	1	0.2
Shortness of breath	5	1.42	Skin infiltration	8	2.28
Tachycardia	2	0.5	Change skin color to blue	6	1.71
Nausea	5	1.42	Reduction of pigmentation	3	0.8
Convulsion	5	1.42	Maculopapular rash	2	0.5
Reduced alertness	4	1.14	papilledema	6	1.71
Reduced vision	4	1.14	Cerebral Palsy	2	0.5
Confusion	3	0.8	Central nervous system involvement	3	0.8
Cerebral Palsy	1	0.2	Testicular pain	1	0.2
insomnia	1	0.2	Itch	3	0.8
Dysuria	7	2.00	Flank pain	4	1.14
Sputum	5	1.42	Anuria	2	0.5
Earache	5	1.42	Polyuria	2	0.5
Vertigo	5	1.42	Urine dribbling	1	0.2
Dizziness	4	1.14	Urinary incontinence	1	0.2
Pleural effusion	2	0.5	Chest pain	8	2.28
Decreased breath sounds	2	0.5	Facial swelling	8	2.28
Hearing loss	1	0.2	Orthopnea	6	1.71
Tea-colored urine	7	2.00	Hand and foot edema	3	0.8
Bruising easily	6	1.71	Mediastinum Mass	4	1.14

and prolonged tachycardia, heart murmur, and pale eyes (14). In this study, headache, heart murmur, and anxiety were reported as common clinical findings. If anemia is not a consequence of inadequate production of erythrocytes, it will be due to blood loss such as epistaxis, gingival, or GI bleeding because of thrombocytopenia (15, 16). In our study, epistaxis and gingival bleeding have also been reported.

Brain involvement may appear in the form of nausea, vomiting, seizure, decreased level of consciousness, confusion, cerebral palsy, insomnia, and visual impairment (17-19). In this study, vomiting, nausea, seizure, decreased level of consciousness, and visual impairment were also reported as symptoms.

A decrease in granulocyte count will prone patients to infections, especially GI and respiratory tract. Furthermore, some diagnostic and therapeutic procedures themselves could be a site of infection (i.e., bone marrow aspiration and catheterization). The most common pathogens in ALL are gram-negative bacilli and later gram-positive cocci, such as Staphylococcus aureus and Staphylococcus epidermidis (20-23). To prevent infections, we can use prophylactic antibiotics.

Skin involvement is not very common and presents with various types of ulcers that may be exclusively filled with cancerous cells, or non-specific ones, similar to erysipelas, eczema, and skin color changes. In the biopsy, severe infiltration of cancer cells around the blood vessels in the epidermis and subcutaneous tissue can be seen (24, 25). In this study, yellow discoloration, skin infiltration, such as maculopapular rash, were reported. Therefore, a skin biopsy may be useful in early diagnosis of leukemia.

The first manifestations of leukemia with a CNS involvement are not very common, including pupil edema with evidence of an increase in intracranial pressure with morning vomiting and unexplained headaches and cerebral palsy that may appear for the first time (26, 27). Some studies have reported that involvement of the CNS at diagnosis in children with ALL T-type significantly correlates with high mortality in patients (28). In the present study, only 3.3% of patients presented pupil edema, cerebral palsy, and other CNS involvement.

In the population of this study, a large percentage of patients with organomegaly were observed. Hepatomegaly, lymph nodes enlargement, and splenomegaly were the most prevalent in patients. Some patients presented the disease with a mass in mandible and edema, or a mass in neck and face edema, and also orthopenia and orbital edema. The cancerous cells infiltration in the liver, spleen, lymph nodes, and mediastinum shows itself as hepatomegaly, splenomegaly, or a mass in mediastinum. According to some studies, the reason for splenomegaly (as an antibody source) could be the sedimentation of antibodies against leukemic cells in the spleen and infiltration of the leukemic cells (29-32).

Finally, it can be noted that the interpretation of clinical symptoms, along with laboratory findings, especially cytogenetic, molecular, and flow cytometry results, is definitely more valuable. A careful examination of unusual and common clinical symptoms in children, along with cytogenetic and molecular results, is suggested to help early and accurate diagnosis.

CONCLUSION:

Our results showed that there are some obstacles to early diagnosis of ALL. Therefore, many patients are missed in the early stages. In conclusion, physicians can consider the symptoms that appear simple and general or non-specific at first glance, as clues and suggestions for the diseases and take the necessary measures to diagnose the disease and eventually save the patient's life. Uncommon signs and symptoms in physical examination or history taking should not be missed as rare presentations in the differential diagnosis of the disease.

Conflict of Interest:

The authors report no conflicts of interest.

REFERENCES:

1. Siegel RL MK, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin. 2017;67(1):7-30.
2. Amori N, Aghajani M, Asgarian F, Jazayeri M. Epidemiology and trend of common cancers in Iran (2004–2008). European journal of cancer care. 2017;26(5).
3. Chiaretti S, Zini G, Bassan R. Diagnosis and subclassification of acute lymphoblastic leukemia. Mediterranean journal of hematology and infectious diseases. 2014;6(1).
4. Pui C-H. Recent research advances in childhood acute lymphoblastic leukemia. Journal of the Formosan Medical Association. 2010;109(11):777-87.
5. Armstrong SA, Look AT. Molecular genetics of acute lymphoblastic leukemia. Journal of Clinical Oncology. 2005;23(26):6306-15.
6. Richardson RB. Promotional etiology for common childhood acute lymphoblastic leukemia: the infective lymphoid recovery hypothesis. Leukemia research. 2011;35(11): 1425-31.
7. Hjalgrim LL, Rostgaard K, Schmiegelow K, Söderhäll S, Kolmannskog S, Vettenranta K, et al. Age-and sex-specific incidence of childhood leukemia by immunophenotype in the Nordic countries. Journal of the National Cancer Institute. 2003;95(20):1539-44.
8. Whitlock JA. Down syndrome and acute lymphoblastic leukaemia. British journal of haematology. 2006;135(5):595-602.
9. Shih TY, Wu J, Muo CS, Kao CH. Association between leukaemia and X-ray in children: A nationwide study. Journal of paediatrics and child health. 2014;50(8):615-8.
10. Stepina V, Gurtsevich V, Morozova L, Etkin A, Urazova L. Human acute lymphoblastic leukemia associated with HTLV-I virus and its infection in healthy populations from various regions of the USSR. Eksperimental'naia onkologiia. 1987;9(3): 32-3.
11. Conter V, Aric M, Basso G, Biondi A, Barisone E, Messina C, et al. Long-term results of the Italian Association of Pediatric Hematology and Oncology (AIEOP) Studies 82, 87, 88, 91 and 95 for childhood acute lymphoblastic leukemia. Leukemia. 2010;24(2):255-64.
12. Castro-Jiménez MÁ, Rueda-Arenas E, Daladier Cabrera-Rodríguez M. Approach to prediagnostic clinical semiology, noticed by mothers, of childhood acute lymphoblastic leukemia. Arch Argent Pediatr. 2015;113(4):331-6.
13. Amanda Ibagy DBS, Jackline Seiben, Ana P.F.F. Winneshoffer, Tatiana E.J.B. Costa, Juliana S. Dacoregio, Imaruí Costa, Daniel Faraco. Acute lymphoblastic leukemia in infants: 20 years of experience. Jornal de Pediatria. 2013;89(1):64-9.
14. Steele M, Narendran A. Mechanisms of defective erythropoiesis and anemia in pediatric acute lymphoblastic leukemia (ALL). Annals of hematology. 2012;91(10):1513-8.
15. Barbui T, Finazzi G, Falanga A, Battista R, Bassan R. Bleeding and thrombosis in acute lymphoblastic leukemia. Leukemia & lymphoma. 1993;11(sup2):43-7.
16. Gorosquieta A, Pérez EE, Gastearena J. Asymptomatic pathological rupture of the spleen as the presenting form of acute lymphoblastic leukemia. Sangre. 1996;41(3):261.
17. Patiroglu T, Unal E, Karakukcu M, Ozdemir MA, Tucer B, Yikilmaz A, et al. Multiple fungal brain abscesses in a child with acute lymphoblastic leukemia. Mycopathologia. 2012;174(5-6):505-9.
18. Levy JMM, Hunger SP. Brain size and neuropsychological functioning in long-term survivors of pediatric acute lymphoblastic leukemia. Translational pediatrics. 2013;2(4): 140.
19. Nadaraja S, Mamoudou AD, Thomassen H, Wehner PS, Rosthoej S, Schroeder H.Palonosetron for the prevention of nausea and vomiting in children with acute lymphoblastic leukemia treated with high dose methotrexate. Pediatric blood & cancer.2012;59(5):870-3.
20. O'Connor D, Bate J, Wade R, Clack R, Dhir S, Hough R, et al. Infection-related mortality in children with acute lymphoblastic leukemia: an analysis of infectious deaths on UKALL2003. Blood. 2014;124(7):1056-61.
21. Graubner UB, Porzig S, Jorch N, Kolb R, Wessalowski R, Escherich G, et al. Impact of reduction of therapy on infectious complications in childhood acute lymphoblastic leukemia. Pediatric blood & cancer. 2008;50(2):259-63.
22. Alados J, Cobo F, Jiménez M, Jurado M, De Cueto M, Miranda C, et al. Catheter infection by Mycoplasma hominis in a patient with acute lymphoblastic leukemia. Enfermedades infecciosas y microbiologia clinica. 1998;16(5):252-.
23. Krauze A, Krenke K, Matysiak M, Kulus M. Fatal course of pulmonary Absidia sp. infection in a 4-year-old girl undergoing treatment for acute lymphoblastic leukemia. Journal of pediatric hematology/oncology. 2005;27(7):386-8.
24. Su WD, Buechner S, Li C-Y. Clinicopathologic correlations in leukemia cutis. Journal of the American Academy of Dermatology. 1984;11(1):121-8.
25. Cho-Vega JH, Medeiros LJ, Prieto VG, Vega F. Leukemia cutis. American Journal of Clinical Pathology. 2008;129(1):130-42.
26. Sison EAR, Silverman LB. CNS prophylaxis in pediatric acute lymphoblastic leukemia. ASH Education Program Book. 2014;2014(1):198-201.
27. Rivera G, Mauer A, editors. Controversies in the management of childhood acute lymphoblastic leukemia: treatment intensification, CNS leukemia, and prognostic factors. Seminars in hematology; 1987: Elsevier.
28. Rives S EJ, Camós M, García-Miguel P, Verdeguer A, Couselo JM, Tasso M, Molina J, Gómez P, Fernández-Delgado R, Navajas A, Badell I; grupo cooperativo SHOP (Sociedad Española de Hemato-Oncología Pediátrica). [T-cell pediatric acute lymphoblastic leukemia: analysis of survival and prognostic factors in 4 consecutive protocols of the Spanish cooperative study group SHOP]. Med Clin (Barc). 2012;139(4):141-9.
29. Saison J, Berger F, Lebosse F, Audoual R, Thomas X, Michallet M. Hepatomegaly and fever at the time of neutrophil recovery revealing L-asparaginase toxicity in the

treatment of acute lymphoblastic leukemia. The American journal of case reports. 2014;15:13.

30. Ozsoylu S, Hiçsönmez G, Koçak N, Zamani V. Isolated splenomegaly during remission in childhood acute lymphoblastic leukemia. The Turkish journal of pediatrics. 1984;27(4):219-23.
31. Friedman A, Schauer P, Mertelsmann R, Cirrincione C, Thaler H, Dufour P, et al. The significance of splenomegaly in 101 adults with acute lymphoblastic leukemia (ALL) at presentation and during remission. Blood. 1981;57(4):798-801.
32. Simone JV, Verzosa MS, Rudy JA. Initial features and prognosis in 363 children with acute lymphocytic leukemia. Cancer. 1975;36(6):2099-108.