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EXTRAMEDULLARY SYMPTOMS AT THE INITIAL PRESENTATION OF ACUTE LYMPHOBLASTIC LEUKEMIA IN CHILDREN

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy with variety of nonspecific symptoms that may present with signs and symptoms related to extramedullary involvement, therefore, leads to delayed diagnosis of ALL in children. Aim: This study aims to determine the prevalence of extramedullary manifestations at the initial presentation of acute lymphoblastic leukemia in children. Method: This is a retrospective, cross-sectional study assessing medical records of 73 patient newly diagnosed (ALL) at Almaty Scientific center of pediatrics and surgery during-2020. The children had a mean age of 6.9 ±4.27 years. The female and male patients made 46 (63 %) and 27(37 %) respectively. children with acute lymphoblastic disease were classified into two subtypes (B-cell ALL and T-cell ALL) according to the WHO classification. Data earned from the study were enrolled within a directory also statistical analysis was done by applying the software (SPSS) version 26.0. Categorical variables resembled using the chi-square test or Fisher's exact test, as appropriate. Result: In this study, the most common extramedullary initial signs and symptoms of ALL were related to hepatic system 49 (67.1 %) and gastrointestinal symptom 43 (58.9%).The additional extramedullary presentations of ALL in order of frequency include; lymphadenopathy 20 (27.4%) , musculoskeletal system 19 (26%) urinary system 9 (12.3 %), Respiratory 9 (12.3 %) , Neurological system 5 (6.8%) orbital presentation 3 (4.1%), neurologic signs 8 (9%%), pericardial involvement 1 (1.4%), and the other miscellaneous presentations 3 (4.1%).Conclusion: This study showed that a significant number of ALL patients present with variety of extramedullary symptoms that pediatrician must become familiar with those to detect some atypical cases of leukemia early on. And increase the probable chance of survival by early detection.

Key words: ALL, unusual presentation, extramedullary presentation of ALL, children.

Introduction

Acute lymphoblastic leukemia (ALL) accounts for about 25% of all the childhood malignancies and is the most usual form of cancer in children which is five-fold greater than acute myeloid leukemia in children [1]. In the United States, the ALL incidence was anticipated 3.4 cases per 100000 children; with around 2500 to 3500 new cases in children each year. As a whole, 15% of ALL was initiated by T-cells, 85% by B-precursor cells, and 1% by NK cells. The male-to-female ratio is around (1.2:1). Children ages 2 to 5 have the most age-related incidence [2].

Depending on whether blast cells have invaded the extramedullary tissue or not, different clinical manifestations of ALL occur. ALL can affect any organ or tissue by the abnormal cells; in spite of the actuality it typically affects the bone marrow and peripheral blood [3].

The most usual manifestations of ALL are often because of a failure in bone marrow (BM); including anemia, Leukopenia and thrombocytopenia. Therefore, the patients might be presented with purpura, petechial, anorexia, and tiredness, pain in bones usually in large bones, fever and pallor. And these mentioned symptoms are connected to medullary contribution [4].

Leukemiccellinfiltrationcangenerateextramedullary signs such as inactive and silent lymphadenopathy and liver enlargement in 68% of children. Additionally, the struggle of the skin, kidneys, eyes, and liver needs to be taken into account. Any of these symptoms that remain for a long time and frequently might be cancerous. Increased cerebral pressure, headache, disorientation, vomiting, and stiffness in the neck are all symptoms of CNS involvement. In rare cases, trigeminal neuralgia, Bell's palsy, and neuropathy may also coexist with the ALL [5].

About 2 percent of boys with ALL will have enlarged testicles at the time of first evaluation, which may also include liver and mediastinal mass hypertrophy and leukocytosis [6].

A joint or bone discomfort, or bone fracture is the most common muscle and bone sign of childhood leukemia, which exists in forty percent of children. If doctors pay close consideration to non-articular discomfort, greater LDH, and blasts in peripheral circulation suggesting ALL, such cases that are difficult to diagnose can be lowered [7].

Extramedullary invasion is extremely infrequent at the beginning of the manifestation and includes the ocular, renal, liver, abdominal, bladder, mouth, pericardium, and pancreas [8].

The purpose of this study is to figure out the prevalence of extramedullary representations at the initial onset of acute lymphoblastic leukemia in children and to familiarize healthcare professionals with the extramedullary manifestations of ALL in children in order to prevent postponed diagnosis and possibly boost the likelihood of a survival margin through detection at an early stage.

Materials and Methods

This is a retrospective, cross-sectional research that analyzed the medical records of 73 newly identified (ALL) patients at Almaty Scientific Center of Pediatrics and Surgery from January 1 to December 31, 2020. The children's mean age was 6.9 ± 4.27 years. Children with acute lymphoblastic disease were classified into two subtypes (B-cell ALL and T-cell ALL) according to the WHO classification. Data earned from the study were enrolled within a directory also statistical analysis was done by applying the software (SPSS) version 26.0. The descriptive statistics were provided in the form of a mean, standard deviation, frequency, and ratios, as well as relevant table and chart representations. Also, all patients' abdomen ultrasound scans obtained at the moment of diagnosis were evaluated for lymphadenopathy, organomegaly, cystitis, ascites, renal lithiasis, liver infection, along with other findings that were unusual in the initial stages of the illness.

Inclusion and exclusion criteria: The candidates meeting the inclusion criteria included every child who was initially identified with acute lymphoblastic leukemia at the Almaty Scientific Center of Pediatrics and Surgery in 2020.ALL Patients with the conditions listed below were excluded:

- Children with HIV/AIDS
- Children with Down syndrome
- Children with insufficient information

Main variables in quantitative analysis: The ages, genders, living areas and districts of the patients, subtypes of ALL, very first compliances of various organs (gastrointestinal, Hepatic, Lymphatic, Neurological, Renal, Ophthalmic, Respiratory, Earing, Cardiac, Genital, and Musculoskeletal), and unusual findings of ultrasound of the abdominal region during the initial stages of the illness were all considered during the research.

Results and Discussion

Medical record of 73 newly diagnosed ALL at Almaty Scientific center of pediatrics and surgery during 2020 was systematically reviewed. 46 (63 %) patients were female and 27 (37 %) patients were male. Age varied between 0.11 and 16 years (average 6.978 years). The highest incidence of ALL was between ages 2-9 years (figure1). The patients came from seven distinct areas and 23 various municipalities throughout Kazakhstan. Our patients were mostly from Almaty and Turkistan (45.2% and 15.1%) respectively, with the fewest coming from West Kazakhstan.

In this study, the most common extramedullary initial signs and symptoms of ALL were related to hepatic system 49 (67.1 %) and gastrointestinal symptom 43 (58.9%).The other extramedullary presentations of ALL in order of frequency include; lymphadenopathy 20 (27.4%), musculoskeletal system 19 (26%) urinary system 9 (12.3 %), Respiratory 9 (12.3 %) , Neurological system 5 (6.8%) orbital presentation 3(4.1%) , neurologic signs 8 (9%%), pericardial involvement 1 (1.4%), and the other miscellaneous presentations 3 (4.1%).

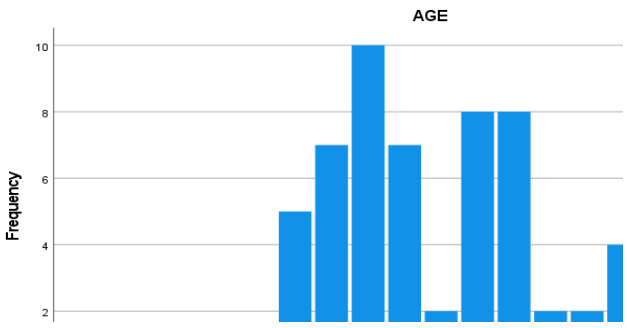

Figure 1 – Frequencies of ALL at different age in children

In this study, gastrointestinal manifestations were described only at the initial presentation of ALL. Gastroenteritis is a main reason of pediatrics diarrhea and greatest usual causes is viruses, particularly in developing countries. Vomiting, nausea and diarrhea are nonspecific symptoms in childhood and is important to cautiously assess these patients for absence of organic illnesses. In this study, diarrhea was present in 15.1% of patients (female=19.6% male=7.4%). Constipation was present in 5.5% (female=6.5% male=3.7%). In the pediatric population without AL this complaint is responsible for 3% and 25% of pediatric and gastroenterological pediatric office visits [9]. Nausea and vomiting was present at 24.7% (female=21.7% male=29.6%) and abdominal pain was seen in 23.3 %. Vomiting and abdominal pain are symptoms that may arise from a number of different causes. Only 5% to 10% of patients have a defined etiology.

Common causes of acute abdominal pain include gastroenteritis, appendicitis, intussusception, incarcerated hernia, cholecystitis, urinary colic and pancreatitis, diverticulitis [10]. In this research, ascites was found in 17.8% of patients (female=21.7%, male=11.1%). 16.4% of patients experienced abdominal distention, and 1% experienced intestinal bleeds. On assessment, over 50 percent of children with leukemia had palpable liver and spleen. Anorexia, stomachache, and distension of the abdomen were common abdomen manifestations. patients with unknown sickness necessitate a thorough assessment, and the presence of several symptoms and signs should alert doctors to the possibility of leukemia [11].

Arthritis in the knee, Limping, and Hip joint arthritis were the most common musculoskeletal complaints in our research (26%). According to the data, ALL with joint manifestations is commonly observed (18.5%). The diagnostic latency in patients with joint involvement might be twice as long as in those without. Previous research has shown that the peculiar manifestation among children with musculoskeletal involvement caused delayed diagnosis [12].

In our study, the prevalence of urinary organ disorders was 12.3, which included calculi in the renal system, hematuria, Nephromegaly, and cystitis. And Nephromegaly was more common. Nephromegaly occurs in varying degrees in ALL individuals. Several studies claim that it ranges between 2 and 24%. Urinary lithiasis is common in T-ALL and appears in conjunction with spontaneous tumor lysis syndrome [13].

In our study, 67.1% of children with ALL had hepatic manifestations. Hepatomegaly was the particularly common primary presenting sign (41.1%), and it was more common in males. And hepatitis was the second most common liver manifestation (17.8%), while jaundice was detected at (8.2%), which was more common in females. Hepatomegaly affects around one-third of patients and is commonly associated with splenic association in 68% of events. Hepatomegaly is one of the most prevalent presenting manifestations in AL as a hallmark of extramedullary leukemia expansion, and it often goes silent [14].

ALL's neurological manifestations include neuropathy (acute sciatica, trigeminal neuralgia, and facial palsy), intracranial lesions, and myopathy [15]. As a result, neuropathy was identified as a cause of the extramedullary neurological symptom of ALL in our investigation. In this investigation, the prevalence of neuropathy was 1.4% (with just one patient having Fascial neuritis). Other studies have revealed that neuropathy affects roughly 0.6% of the population [16].

The prevalence of orbital symptoms as an extramedullary first presentation in ALL was 4.1% in this research, which included retinal detachment and dry eye. In previous research, the prevalence of orbital presentations as an extramedullary first manifestation in ALL was 11.5%, including intra-orbital masses, optic nerve disease, decreased eyesight, and detached retinas. The reasons for visual impairment and optic nerve swelling in children with ALL are undiscovered although it is thought to be due to fluid drainage blockage caused by leukemic cell perivascular infiltration. T – ALL was associated with more frequent vision impairment and visual nerve edema [17]. Another preclinical sign of ALL is the leukemic invasion of the choroid and detached retina, which can be linked to choroid hyper vascularity [18].

In the present research, (1.4%) of the participants had a cardiovascular manifestation as their very first sign of ALL, such as pericardial fluid accumulation in a 4-year-old girl with T-cell ALL (Tabl.1). In a previous investigation, pericardium involvement referred to as a manifestation of ALL was detected in (2.3%) of patients. Pericardial effusion, pericarditis, and cardiac tamponed have all been reported as a result of leukemic infiltration [19].

Table 1 – Frequency of extramedullary symptom as initial presentations of ALL

Locations	Total N (%)	F:M Ratio	Mean of ages (y) ± SD	Test of difference		
				χ2	D.f	p-value
Hepatic	49 (67.1)	0.8:1	7.2±3.6 (2-15)	0.290	1	1.118
Gastrointestinal	43 (58.9)	1.3:1	7.1±4.1 (0.11-16)	2.048	1	0.152
Lymphadenopathy	20 (27.4)	1.09:1	8.5±4 (3-16)	0.665	1	0.415
Musculoskeletal	19 (26.0)	1.01:1	7.4±4 (1.6-16)	0.001	1	0.988
Knee joint arthritis	3					
Limping (LEP)	15					
Hip joint arthritis	1					
Renal	9 (12.3)	1.17:1	4.9±4.2 (0.9-15)	0.059	1	0.808
Nephromegaly	7					
Cystitis	2					
Hematuria	1					
Urine lithiasis	1					
Respiratory	9 (12.3)	0.3:1	6±4 (2-14)	3.880	1	0.49
Cough	5					
Pneumonia	3					
Nasopharyngitis	1					
Neurological	5 (6.8)	0.4:1	6.2±1.9 (3-8)	1.220	1	0.269
Headache	4					
Fascial neuritis	1					
Ophthalmic	3 (4.1)	0.3:1	9.3±2.3 (8-12)	1.183	1	0.277
Retinal detachment	2					
Dry eye	1					
Genital	2 (2.7)	0: 1	11.5±4.9 (8-15)	3.503	1	0.061
Orchitis	2					
Earing	1 (1.4)	2.2:0	2 (2-2)	0.595	1	0.440
Otitis media	1					
Cardiac	1 (1.4)	2.2:0	4 (4-4)	0.595	1	0.440
Pericardial effusion	1					

Twenty patients (27.4%) experienced lymphadenopathy, which was more common in the parotid and cervical regions and less so in the inguinal region. In previous research, most patients exhibited palpable lymphadenopathy and hepatosplenomegaly, which was identified in half of the children, and hepatosplenomegaly was discovered in the remaining 25% of participants [20].

Significant lymphadenopathy and hepatosplenomegaly were observed in 12.3% of the individuals in our study, with hepatosplenomegaly identified in the remaining 41.1%. This demonstrates that roughly 50% of ALL suffers may be detected with a history-taking and medical checkup of the lymph nodes, liver, and spleen.

Sonography of the abdomen showed the following findings in the patients at the moment of evaluation; hepatomegaly in 49 of the cases (67.1%), splenomegaly in 43 cases (58.9%), hepatosplenomegaly in 39 (53.4%), lymphadenopathy in 20 (27.4%), ascites in 13 (17.8%), nephromegaly in 7 (9.6%), pancreatic change in 5 (6.8%), cystitis in 2 (2.7 %),Urinary lithiasis in 1 (1.4 %) of the patients (Tabl.2).

Table 2 – Abnormal findings in the abdominal ultrasound scanning at the time diagnosis of the disease

Abnormal findings	N	%
1	2	3
Hepatomegaly	49	67.1%
Splenomegaly	43	58.9%
Hepatosplenomegaly	39	53.4%
Lymphadenopathy	20	27.4%
Ascites	13	17.8%

1	2	3
Nephromegaly	7	9.6%
Pancreatic change	5	6.8%
Cystitis	2	2.7%
Urinary lithiasis	1	1.4%

Ultrasonography can easily confirm Organomegaly in patients with ALL. The limitation of sonography is the lack of histologic confirmation of the organomegaly's basis. Invasive approaches such as laparotomy and percutaneous biopsies are avoided in such patients because of the increased risk of challenges. In a sonography examination of children with leukemia, splenomegaly, hepatomegaly, renal enlargement, and lymphadenopathy were seen at 59%, 60%, 18%, and 5% respectively [21]. This is consistent with our results. According to our investigation and previous clinical studies, hepatosplenomegaly and other organomegaly were found in most of the patients. In our investigation, ultrasonography found more accurate pathologic results than physical examination. Hepatomegaly is a typical clinical symptom in ALL as an extramedullary spreading leukemia presentation, and it is often quiet.

Conclusion

This study revealed that a significant number of ALL patients present with variety of extramedullary symptoms and the clinical diagnosis of childhood ALL requires clinical vigilance rather than complex laboratory investigations that pediatrician must become familiar with those todetect some atypical cases of leukemia early on and reduce the due mortality and disability through timely detection.

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