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SYMPTOMS OF EARLY SIGNS OF ACUTE LYMPHOBLASTIC LEUKEMIA IN CHILDREN IN UZBEKISTAN

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Abstract.The article describes the early symptoms of manifestations of acute lymphoblastic leukemia in children. Given that there is no prevention of acute leukemia, early detection and timely initiation of treatment is one of the main conditions for successful treatment and reduction of mortality. This dictates the need to increase the oncological alertness of primary care physicians, development of educational programs for pediatricians, other specialists, as well as for parents in their native language.

Keywords: oncological alertness, children, acute lymphoblastic leukemia, diagnosis

Children's cancer cannot be prevented, but it can be detected early, giving the child a chance at life. Early diagnosis of oncohematological diseases in children is extremely difficult due to the non-specificity of the primary symptoms, which are often hidden under the "masks" of other diseases [1,2,3,4,17]. Oncological alertness and knowledge of probable symptoms will allow the practitioner to diagnose this pathology earlier and, therefore, significantly improve the prognosis for the patient [6,7,8,9,15]. In the structure of childhood leukemia, acute lymphoblastic leukemia (ALL) dominates, accounting for 75-80% of cases [9,10,11,12].

Despite the progress of laboratory diagnostics, it is difficult to detect leukemia in children in the early stages. for the appearance of characteristic changes in the hemogram, the tumor must reach a critical mass [3,4,13], and the manifestation of ALL is associated with blast infiltration of various organs with impaired function [8]. Clinical symptoms in this case are ahead of laboratory changes, and the child is not admitted to a specialized hematological hospital [14,15].

At an early stage of leukemia, a restructuring of hematopoiesis occurs without the involvement of internal organs in the process, i.e. in the bone marrow, a clone of tumor cells is only formed without their metastasis. There are no definite clinical symptoms manifest for this stage (F.E. Fainshtein et al., 1984; EB Vladimirskaya, 1984). The onset of specific clinical manifestations during the development of OB is associated with an increase in the mass of tumor cells and overcoming the level of 1012-1013 cells [1; 4; 15, 16].

Purpose of the study: to study the nature and frequency of clinical syndromes and diseases-masks of the early period of acute lymphoblastic leukemia in children.

Material and methods. Anamnesis data and case histories of 263 children aged 2 months and older up to 18 years old were analyzed, suffering from acute lymphoblastic leukemia. All children have been undergoing treatment in the children's department of the Scientific Research Institute of Hematology and Blood Transfusion(Tashkent city) since 2008. to 2015.

Research results and discussion.

Analysis of the condition of patients at the initial admission showed that the acute onset of the disease was registered in 221 (84.1%), and was characterized by high fever, severe intoxication, joint and abdominal pain, the presence of changes in the pharynx and nasopharynx.

During a clinical examination of initially admitted children with ALL - 97% (255 patients) had anemia of varying severity, 210 patients (80%) had a concomitant infectious pathology, that is, immunodeficiency syndrome.

Lymphoproliferative syndrome was detected in 198 patients (75.3%) of the majority of those who consulted adoctor; an increase in peripheral lymph nodes was revealed, more often in the form of polylymphadenopathy, without signs of inflammation.

Intoxication syndrome with a gradual onset was observed in 234 patients (89%) and was characterized by the development of nonspecific symptoms: slowly progressive weakness, increased fatigue, flying pains in bones, muscles, joints.

It is common for young children to stop walking. Unfortunately, the diagnosis of ALL was established no earlier, more than 6-8 weeks later after the child's first visit to adoctor, only when blasts or leukocytosis appear in the peripheral blood.

Hemorrhagic syndrome manifested itself in 87 patients (33.1%) with bleeding of various localization: nasal, gingival, gastrointestinal, cerebral, as well as hemorrhagic rashes in the form of bruises and petechiae, hemorrhages in the mucous membranes of the oral cavity, in the sclera of the eyes.

The asymptomatic course of acute leukemia was found in 48 cases (18.3%). In this category of patients, the state of health and general condition was not disturbed, there were no particular complaints. An objective examination revealed only a slight increase in lymph nodes, liver and spleen. The diagnosis was made by chance during the next examination for mild anemia, thrombocytopenia was detected, the diagnosis was confirmed after the results of bone marrow puncture. (Fig. 1)

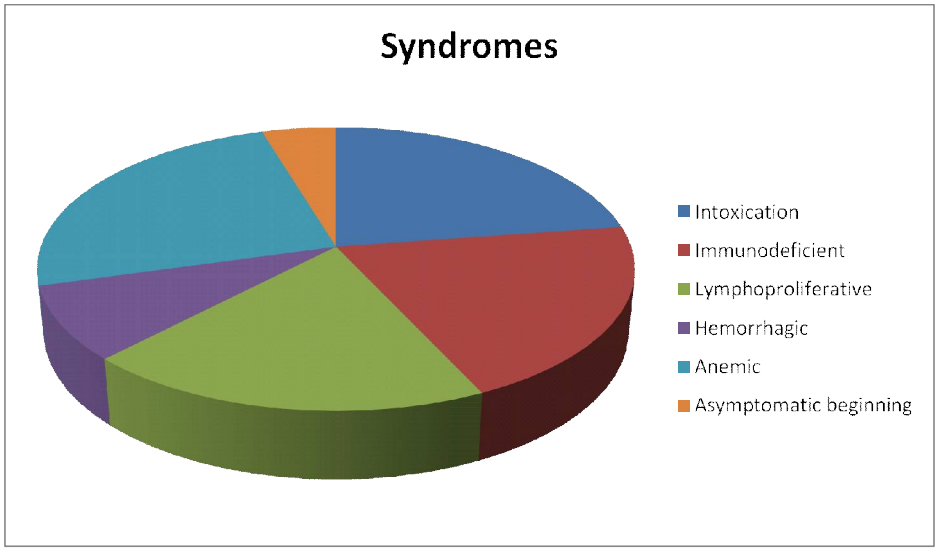

Figure 1. The nature and frequency of the main syndromes of the initial period of acute lymphoblastic leukemia in children

During the initial outpatient visit to the doctor, in some cases at the onset of the disease, the study of a general blood test was carried out late. There is another significant reason for the late diagnosis - despite repeated visits to doctors of different specialties,

only a few doctors, mainly hematologists, prescribed a detailed hemogram with manual counting of cell morphology. At best, the level of hemoglobin, leukocytes and erythrocytes was investigated. When anemia was detected, iron supplements were prescribed, without much effect. In our study, severe anemia was detected in 33% (87 patients), of whom 12% were admitted in an extremely serious condition requiring immediate transfusion of erythrocyte mass. Moderate anemia was observed in 46.7% of cases (123 patients), mild anemia in 52 (19.7%).

The analyzes revealed moderate leukocytosis (up to 30 ? 109/l) - in 99 patients (37.6%), from 30 to 100 thousand - in 78 patients (29.6%), above 100 thousand - 42 (15, 9%), leukocytes were within the normal range in 42 patients (15.9%).

It should be noted that even in the presence of hemorrhagic syndrome, the determination of the number of platelets in the peripheral blood was not carried out at all.At the initial admission with thrombocytopenia below 20 thousand, it was observed in 176 cases (66.9%), from 20 thousand to 50 thousand - in 26 patients (9.8%), and above 50 thousand in 14.8% (39), within the normal range - in 7.9% (21 patients).

The presence of blast cells in peripheral blood was detected in 64.6% (170 patients), increased ESR (erythrocyte sedimentation rate) occurred in 59% of patients (155). (Fig. 2)

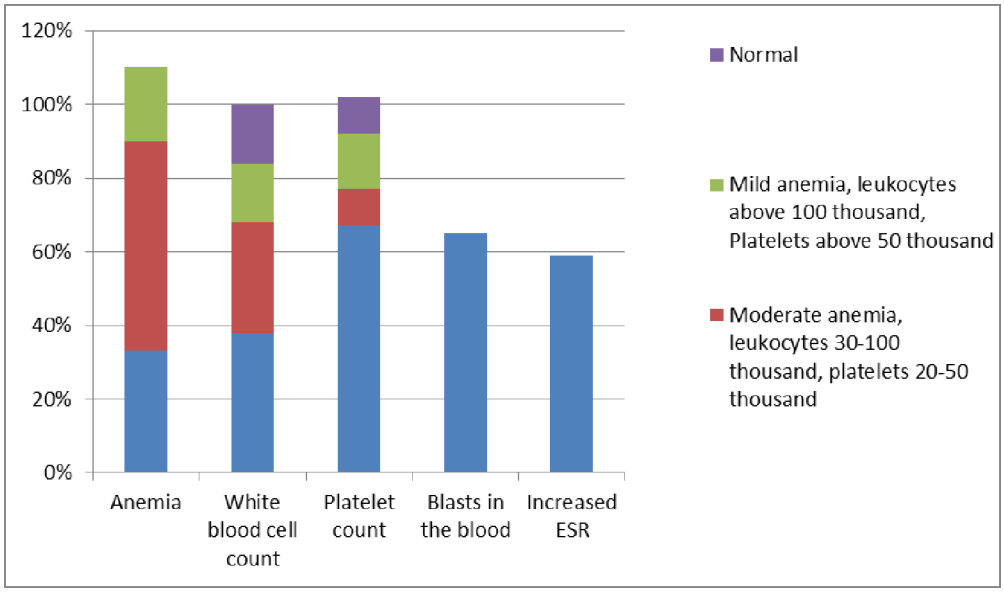

Figure 2. Changes in the hemogram at the initial admission in patients with acute lymphoblastic leukemia.

The defeat of the respiratory and circulatory organs was noted most often (n = 194; 73.7% of children), among which acute bronchitis (24%), pharyngitis, rhinopharyngitis (19.2%), bronchopneumonia (53%) were most often recorded. There was also a lesion of the mediastinal lymph nodes. Patients have shortness of breath, aggravated by physical exertion and in a horizontal position, palpitations, pain in the heart. Determine the expansion of the boundaries of the heart, tachycardia, muffling of tones.

Case study: Patient, G., born in 2003. , was admitted with complaints: according to the mother of weakness, lethargy, frequent dry cough, moodiness, loss of appetite, a sharp pallor of the skin, the appearance of hemorrhages and bruises at the injection sites.

From the anamnesis: According to the parents, the child has been sick for 2 months,

the disease began gradually with weakness, lethargy, moodiness, decreased appetite, and coughing. Received outpatient treatment at the place of residence (a /b therapy; symptomatic therapy). There was no effect of the treatment, the pallor of the skin increased in dynamics, frequent dry cough increased, hemorrhages and bruises appeared at the injection sites. We turned to the oncological center on our own, the district doctor did not give a referral, from there the child was sent for further examination to the consultative clinic of the Hematological Center, where according to the HB-63.0 g/l, platelets -single, leukocytes -300.0 thousand, blasts -93; segmented leukocytes - 4%; lymph-2%; ESR-20 mm/ hour and with a diagnosis of Acute leukemia, 1st active period was hospitalized in the children's department of the Hematological Center.

STATUS PRAESENS: The patient's general condition is extremely serious, the severity of the condition is due to the underlying disease, anemic and hemorrhagic syndrome, severe intoxication and hyperleukocytosis. Consciousness is clear. He reacts uneasily to examination and manipulation.The skin and visible mucous membranes are sharply pale, there are isolated bruises and hemorrhages on the body and at the injection sites. Peripheral lymph nodes of all groups were enlarged to 0.5x0.5 cm. Spleen + 2.0 + 2.5 cm. The lungs auscultation: weakened vesicular breathing, singular. Muffled heart sounds, tachycardia. HR-98/min. Ad-90/60 mm Hg. Art. The belly is round, soft. Liver + 1.5 + 2.0 cm. Stool 1-2 times a day, decorated, without pathological impurities. Diuresis is not impaired. Focal symptoms are not visible. There are no meningeal signs.

Laboratory data: Liquorogram: Cytosis-3; protein - 0.033%;

Myelogram from 06/17/14. CM point is hypercellular. In BM, total blastic metaplasia is noted. GR, KR and MR are reduced. Mgkts- not found. Blasts - 98.6%; lymph. - 1.0;

Cytochemistry: Myeloperoxidase blasts are negative. Blasts glycogen - a positive fine granular form on a pink background. Immunological examination at the Russian Children's Clinical Hospital in Moscow on 06/17/14. Conclusion: Acute lymphoblastic leukemia, T2-variant. Myelogram at the Russian Children's Clinical Hospital, Moscow, dated 06/ 17/14. The BM point is rich in myelokaryocytes, monomorphic in composition, total (96.8%) infiltration of bone marrow by blast cells, which blast cells by morphological characteristics can be attributed to leukemic lymphoblasts of type L1. Normal growths of hematopoiesis are sharply narrowed, practically absent. Mgkts-not found. Conclusion: The bone marrow pattern is consistent with the diagnosis: Acute lymphoblastic leukemia (ALL-L1). Morphological signs of the leukemic population suggest a lymphoid nature.

CT scan of the chest from 06/11/14. Conclusion: CT signs of a mass in the projection of the anterior mediastinum (thymus formation?), Lymphadenopathy of the intrathoracic and peripheral l / nodes. Pericarditis.

Molecular genetic study from 02.07.14 Conclusion: chromosomal translocations were not found.

Based on the foregoing, the diagnosis was made:

Main: Acute lymphoblastic leukemia, T2-variant. 1-active period. Intermediate risk group. PCT course of induction of remission according to the MB-2008 program.

Specific infiltration of the mediastinal organs. Hyperleukocytosis. Hemorrhagic syndrome. Sepsis Bronchopneumonia.

Upper respiratory tract damage occurred in 31% of cases. In most cases, patients with pronounced changes in the nasopharynx were treated by an otorhinolaryngologist for follicular angina, otitis media. Often, with an increase in the submandibular and posterior cervical lymph nodes, palatine tonsils and severe manifestations of intoxication, febrile fever infectious wards. For lymphadenitis, some patients underwent a puncture with the introduction of antibiotics, which subsequently became infected with the development of a submandibular abscess, which significantly worsened the condition of

the patients and the conduct of programmed chemotherapy.

In 29% of cases, acute lymphoblastic leukemia manifested signs of osteoarticular syndrome. Against the background of general poor health, pain in the bones and joints appeared. There was a sharp pain that intensified at night, which dominated the entire clinical picture. From the beginning of such a clinical picture to the diagnosis of acute lymphoblastic leukemia, an average of 2-2.5 months passed. An objective examination revealed soreness in the long tubular bones, soreness and limited mobility in the joints, and often their swelling. This was the basis for the erroneous diagnosis of rheumatism or rheumatoid arthritis and the appointment of steroid hormones in this regard. The intake of corticosteroids led to a smoothing of the symptoms of acute leukemia and subsequently made it difficult to establish the correct diagnosis in a timely manner. Resistance to the therapy, the study of the hemogram with manual counting helped to refer the patient to a consultation with a hematologist. Also, a lesion of the spinal column was noted, as a result of the vertebral bodies due to structural disorders, flattening or fracture of the vertebral bodies occurred in some patients. Sick children stopped walking, severe pain syndrome was observed, at times requiring the administration of potent pain relievers (for example, tramadol). The X-ray picture is mainly represented by the presence of diffuse osteoporosis; more reliable changes could be seen only during the ST of the spine. With a long course of the process, due to late diagnosis due to the progression of the disease, osteolytic foci in the bone tissue grow, leading to fractures. Such cases were observed in 6 patients.

Example from practice: Patient K., born in 2007. Complaints at admission: weakness, fatigue, decreased appetite, pallor, fever, cough, leg pain.

From the anamnesis: Sick for 2 months. The above symptoms were noted; the child was consulted by a traumatologist, an orthopedist, a neurologist, and received numerous outpatient and inpatient treatment, which included corticosteroids. The treatment was ineffective, a detailed blood test was not done, then he was sent to the Research Institute of Pediatrics, from there he was sent to the Hematological Center (Tashkent). The child was hospitalized. Hemogram: HB -94 g/l, Erythr-3.0, Ptl-198.0, leuk. - 3.8, ESR-15 mm/h. Myelogram: CMP is quite cellular, Metaplasia of blasts is noted -92.6%, the red sprout is depressed, the type of hematopoiesis is normalablastic, no megakaryocytes were found. Cytochemistry: Blasts for myeloperoxidase are negative, glycogen is positive, in the form of large granules. Immunophenotyping: CD19 negative acute lymphoblastic leukemia from B-precursors (blasts -45%). CT - chest from 4.06.10: Manifestation of bronchitis. Destruction of bodies and lateral arches of VTh6, VTh7, VTh8. Lymphadenopathy (peribronchial and hilar l / nodes). Based on the above, the diagnosis was made:

Main diagnosis: ACUTE LYMPHOBLASTIC LEUKEMIA, B3 immunovariant, first active period. Concomitant diagnosis.: Poliossal, bilateral fibrous dysplasia of the bodies and lateral arches VTh6, VTh7, VTh8.

The defeat of the gastrointestinal system occurred in 34% of cases. Among the lesions of the gastrointestinal tract, the most common stomatitis (56.0%). In young children, ulcerative-necrotic lesions of the oral mucosa were observed as a result of refusing to eat. An objective examination of the mucous membranes of the cheeks, tongue, lips, with areas of necrosis, and gingival hypertrophy was also noted. Dentists prescribed gargles, topical astringents, and some even got injections into the gum area. Patients were sent to a hematologist's consultation only after the development of bleeding and fever. In young children, an isolated lesion of the digestive tract was a variant of the onset of acute lymphoblastic leukemia. There was vomiting, which was not associated with food intake, symptoms of dehydration, frequent loose stools, pallor, lethargy.

Practical example. Patient I., 4 years old, was admitted for inpatient treatment at the UZNII G and PC

Complaints on admission: fatigue, weakness, loss of appetite, pallor, unstable stool, fever, general anxiety.

From the anamnesis of the disease: Sick for 2 months, there was weakness, pallor, fever, loose stools. We went to the pediatrician, received injections of vitamins and antibiotics. Examination at the place of residence revealed anemia, leukocytosis, blastosis in the hemogram . Was hospitalized in the pediatric department with a diagnosis of acute leukemia.

Objectively: The general condition of the patient is serious. Consciousness is clear. He reacts inadequately to examination and manipulation, crying. The skin and visible mucous membranes are pale, single hemorrhages on the legs. The subcutaneous fat layer is moderately developed.Peripheral lymph nodes are not enlarged.The spleen is enlarged, +2.5 cm. Breathing through the nose, free. Tonsils: not enlarged. In the lungs auscultation: hard breathing, single. The boundaries of the heart are within the age norms. Pulse 105/ min, satisfactory filling and tension. Arterial pressure 90/60 mmHg. Auscultatory peristalsis is preserved. Liver +1.5 cm. Stool once a day, without pathological impurities. The tapping symptom is negative on both sides. Diuresis is not impaired.

According to analyzes: Hemogram: Hem. - 72 g/l; Eryth. - 2.65; platelets- one; leukoc. - 3.2 thousand; blasts - 55%, lymphocytes - 37%, mon. - 1%, ESR - 17 mm/h.

The patient was examined at the Russian Children's Clinical Hospital, Moscow: immunological study: CONCLUSION: Acute lymphoblastic leukemia from B-progenitors with co-expression of the myeloid antigen CD65 and rearrangement of the MLL gene. Myelogram .: blasts - 94.2%, MCC not found, red reduced, blasts for myeloperoxidase neg., For glycogen pos. in the form of large granules. Conclusion. According to morpho-cytochemical characteristics, blast cells are classified as leukemic lymphoblasts. The bone marrow pattern corresponds to the diagnosis: Acute lymphoblastic leukemia (ALL-L1).

Results of molecular genetic research: no chromosomal translocations were found.

The diagnosis was made: Acute lymphoblastic leukemia, from B-precursors with co-expression of the myeloid antigen CD65, 1st active period. Hemorrhagic syndrome. Acute bronchitis. Acute gastroenterocolitis.

There was also a sharp cramping pain in the abdomen. In 4 cases, patients were mistakenly operated on for acute appendicitis. But more often the pain was observed due to severe hepatosplenomegaly, ascites.

CNS lesions were found in only 5% in the form of facial asymmetry associated with facial nerve lesions, headache, and vomiting.

Lesions of the urinary system were detected in 12% of patients in the form of cystitis, pyelonephritis. Skin lesions in the form of leukemides were observed in 6%. (Fig. 3)

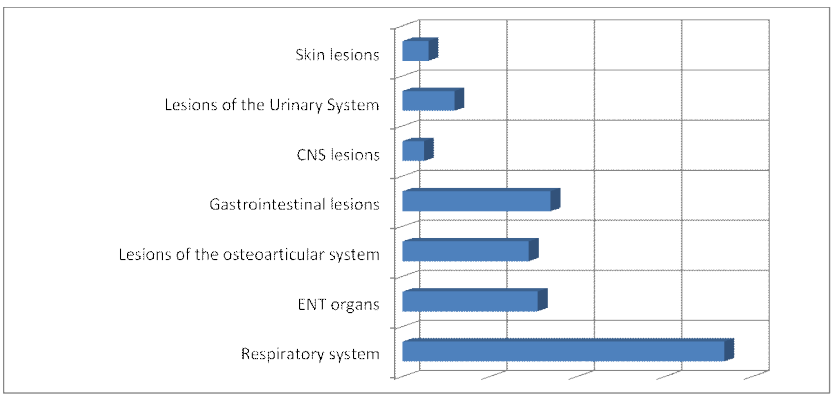

Figure 3. Frequency of damage to organs and systems at the initial admission in patients with acute lymphoblastic leukemia.

Research has shown that the initial symptoms of acute lymphoblastic leukemia in children can vary. This forced the parents to turn to different specialists. Considering the presented cases from practice, we can say about the absence of oncological alertness, both among primary care doctors and other specialists. There were frequent cases of prescribing corticosteroid therapy to a child without preliminary examination of the bone marrow, which led to incorrect and late diagnosis. This led to the fact that patients were admitted in an extremely serious condition with severe infectious complications and pretreated with corticosteroids. This situation often leads to a decrease in the effectiveness of specific anticancer treatment and an increase in the primary mortality rate. The reasons for the diagnostic errors were the absence of a detailed history, neglect of careful examination of the child, and ignorance of the symptoms indicated by the parents.

In recent years, every child with acute lymphoblastic leukemia is considered from the standpoint of complete recovery. The problem of late diagnosis is one of the significant barriers to effective therapy.

Currently, there is also a WHO guide in English for the early diagnosis of childhood cancer, according to which cancer is highly likely in cases where:

1.fever for more than 7 days for no apparent reason;

2.headache: persistent, increasing in dynamics, interrupting the child's sleep, more often in the morning, may be accompanied by vomiting; seizures without fever or neurological disease; one-sided weakness (one limb or one side of the body); asymmetry (facial);

change in consciousness or mental status (change in behavior, confusion); loss of balance when walking; speech disorder;

3.Bone pain, increasing in dynamics for a month or more, reducing the child's activity;

4.petechiae, ecchymosis and / or bleeding; pronounced pallor of the skin of the palms and conjunctiva;

5.leukocoria (a symptom of a "white" eye, a "glowing" pupil); squint that has recently appeared; lack of an iris; different eye color; proptosis (bulging of the eyeballs); visual impairment (double vision, decreased acuity)

6. peripheral lymph nodes> 2.5 cm in diameter, hard, painless, lasting ?4 weeks; palpable mass in the abdomen; hepatomegaly and / or splenomegaly; palpable mass in soft tissues, painless (especially with a diameter of more than 2 cm), without signs of inflammation.

Possible probable signs to look out for, with additional research and referral to a pediatric oncologist:

1.Loss of appetite during the last 3 months;

2.Weight loss in the last 3 months;

3.Weakness within the last 3 months;

4.Night sweats for no apparent reason;

5.Pallor of palms and conjunctiva;

6.Painful lymphadenopathy or lasting <4 weeks, or ? 2.5 cm, or loose consistency;

7.Increase in any part of the body with signs of inflammation.

Conclusions:

Early diagnosis of oncohematological diseases in children depends on many factors, the main ones are: an increase in oncological alertness among primary care physicians and various specialties, their greatest concentration on early diagnosis, an increase in the level of education of the population in the diagnosis and treatment of oncological

diseases, an increase in the medical activity of parents, availability of access to modern diagnostics.

In this regard, it becomes necessary to develop educational programs for pediatricians, other narrow specialists, as well as for parents in their native language on the basis of WHO recommendations using the experience of developed countries.

Used literature.

1.Balasheva I.I., Desyatova L.F. The role of a constitutional factor in clinical polymorphism in children with acute lymphoblastic leukemia. Siberian Journal of Oncology 2012; (6): 64-67.

2.Bulletin of Medical Internet Conferences (ISSN 2224-6150) 2015. Vol. 5. No. 8, 1099, Review Yuditskiy AD, Isakova LS, Eliseeva EV Early diagnosis of acute lymphoblastic leukemia in children.

3.Pediatric hematology / oncology. ed. Rumyantseva A.G., Samochatova E.V. M .: ID MEDPRACTICA, 2004; 792 s.

4.Malignant neoplasms of hematopoietic and lymphoid tissue in children. A guide for doctors. ed. L. A. Durnova. M .: Medicine, 2001.

5.Kaznacheev K.S. Complex issues of early diagnosis of acute leukemia in children. NSU Bulletin. Series: Biology and Clinical Medicine 2011; 9 (2): 211-214.

6.Loria S. S., Rumyantsev A. G., Derbeneva L. I. Some predictive characteristics of acute lymphoblastic leukemia in adolescence // Hematology and transfusiology. 2001. No. 2. P. 24-28.

7.Metkevich G.L., Mayakova S.A. Leukemia in children. Moscow: Practical Medicine, 2009; 384 s.

8.Odinets Yu.V., Panfilova E.A., Panfilov K.V. Debut "masks" of acute leukemia in children. Child Health 2008; (3): 37-41.

9.Chen M., Lin H., Yi C., et al. Typhlitis as the Initial Presentation of Acute Lymphocytic Leukemia - A Case Report. Tzu Chi Med J 2006; 18 (2): 133-136.

10.Duarte-Salazar C., Santill?n-Chapa C., Gonz?lez-Rosado G., et al. Arthritis: an unusual and anticipatory clinical presentation of pediatric acute lymphoblastic leukemia. A case report. Circulation 2012; 80 (5): 455-458. Bulletin of Medical Internet Conferences (ISSN 2224-6150) 2015. Volume 5.

11.Gilboa N., Lum G., Urizar R. Early renal involvement in acute lymphoblastic leukemia and nonHodgkin's lymphoma in children. J Urol 1983; 129 (2): 364367.

12.Gupta N., Gupta S., Rathi S., et al. Acute lymphoblastic leukemia presenting as non-oliguric renal failure and hypertension. Leuk Res 2010; 34 (7): 150151.

13.Karachunskiy A., Herold R., Stackelberg A. von. Results of the First Randomized Multicenter Trial on Childhood Acute Lymphoblastic Leukaemia in Russia // Leukemia. 2008. Vol. 22, No. 6. P. 1144-1153.

14.Kumar R., Walsh A., Khalilullah K., et al. An unusual orthopedic presentation of acute lymphoblastic leukemia. J Pediatr Orthop B 2003; 12 (4): 292-294.

15.Pui C.-H. Acute lymphoblastic leukemia. In: Childhood leukemias. C.H. Pui (ed.), 2nd ed. Cambridge University Press, 2006.

16.Robazzi T., Barreto J., Silva L., et al. Osteoarticular manifestations as initial presentation of acute leukemias in children and adolescents in Bahia, Brazil. J Pediatr Hematol Oncol 2007; 29 (9): 622-626.

17.Sinigaglia R., Gigante C., Bisinella G., et al. Musculoskeletal manifestations in pediatric acute leukemia. J Pediatr Orthop 2008; 28 (1): 20-28.