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CLINICAL MASKS OF ACUTE LEUKEMIA IN CHILDREN

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Abstract: For the study of initial clinical signs of acute leukemia in children 92 case histories have been analyzed. Among them acute lymphoblastic leukemia was in 81.5% of cases and acute myeloid leukemia was in 18.5% of cases. In most children the disease manifested with intoxication (94.6 ± 2,3%), lymphadenopathy (84,8±4,7%), hepatosplenomegaly (96,7±2,3%), anemic (82,6±4,9%), haemorrhagic (77,2±5,4%) syndromes. However, only in half of the cases the correct diagnosis was established in period less than 2-3 weeks since the first symptoms appeared. Consequently, it is necessary to pay attention of general practitioners to the variety of non-specific initial symptoms of acute leukemia in children.

KeyWords: acute leukemia, children, diagnostics, clinical symptoms.

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INTRODUCTION

Acute leukemia (AL) still remains to be one of the challenges in pediatric hematology due to increasing prevalence of the disease, severity, difficulties in early diagnosis of the disease. AL takes a leading place among cancers in children. According to the Bulletin of National Cancer Registry of Ukraine "Cancer in Ukraine" (2014-2015) [1] it is almost one third (29.3 %) of all cancer diseases in children with the incidence rate of 4.5 per 100,000 childhood population. Among them lymphoblastic forms constitute 80-90%. Modern capabilities of chemotherapy can achieve a high level of treatment and survival in patients with leukemia which is a potentially fatal disease. According to the Surveillance, Epidemiology and End Results (USA, 2016) [2] five-year survival rate of children with acute leukemia increased from 36.5% to 85.4% from 1975 to 2012. In Ukraine five-year survival rate is 75-80% in children with acute lymphoblastic leukemia, and it is 40-45% in those with acute myeloid leukemia.

However, variable initial signs of AL can complicate diagnosis at early stages. As a result it leads to late start of treatment.

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2 PURPOSES, SUBJECTS AND METHODS:

2.1 Purpose

The aim of the research was to study the initial clinical manifestations of acute leukemia in children and to improve methods of early diagnosis for timely start of therapy.

2.2 Subjects & Methods

The study involved the assessment of 92 case histories of children aged from 6 months to 18 years. All these children were treated at the hematology department of Kharkiv City Children's Clinical Hospital No.16 with diagnosis of acute lymphoblastic leukemia (81.5% of patients) and acute myeloid leukemia (18.5%). Among them were 58 boys and 34 girls.

AL diagnosis included morphological, immunophenotypical analysis of blast cells and cytogenetic analysis. Most patients (83.9%) with acute lymphoblastic leukemia (ALL) had B-lymphoblastic form. Among them 70.97% had B type, common ALL and 12.93% had pre-B ALL. T-lymphoblastic forms of ALL were diagnosed in 16.1% of children. Other patients had myeloid forms of AL. There were 6 children with M4 variant, 4 children with M1, 2 children with M0, 2 children with M2, 2 children with M5 and one child with M3 variant.

Treatment of patients was performed by BFM protocols (Berlin - Frankfurt - Munster) adapted for Ukraine. Children with newly diagnosed ALL were treated with standard

doses of drugs according to the program ALL IC-BFM -2009, and those with AML were treated according to AML-BFM - 98/2000 protocol.

Conflict of interests

There is no conflict of interests.

3   RESULTS AND DISCUSSION

Significant polymorphism and variability of symptoms in children and adolescents under investigation were typical for clinical manifestation of AL.

Among observed patients there were 34.2±5.4 % of girls and 65.8±5.4 % of boys. Analysis of the distribution of patients showed that boys had AL significantly (p=0.0004) more frequently (Tab. 1). The disease started at the age less than 8 years in 48.9±5.7% of cases. At the same time the most severe AL course was observed in boys at adolescence.

Table 1.

Distribution of AL patients by age at the moment of diagnosis

Statistical parameter	Total	Age, years		
		2-7	8-14	15-18
Absolute Number	92	45	36	11
p% ± Sp%	100	48.9± 5.7	39.2± 5.5	11.9± 3.5

Assessment of medical history showed that the diagnosis was most typically determined within the period of 2 weeks to 2 months on average since first clinical examination. More than half of lymphoblastic leukemia cases (52.0%) were diagnosed in the period of 2-3 weeks since the first signs. Myeloid leukemia was diagnosed in 2-3 months on average. In 15.4% of patients with leukemia diagnosis was not made for the whole year. In 53.9 ± 5.7% of cases there were errors in early diagnosis of acute leukemia. It was more commonly confused with infectious diseases (31.7 ± 7.2%), anemia (26.8 ± 6.9%) and thrombocytopenia (17.1 ± 5.8%). Less commonly initial diagnosis included lymphadenopathy (12.2 ± 5.1%) only instead of ALL, rheumatic diseases (4.9 ± 3.3%), Henoch-Schönlein

purpura (4.9 ± 3.3%) and "acute abdomen" (2.4 ± 2.2%). All these mistakes in timely diagnosis resulted in later start of treatment. It is important to note that the four of the observed children were established to have another cancer disease. One of them had ALL, but he underwent surgical removal of a testicle due to the wrong diagnosis of low differentiated carcinoma of testicle. Another one underwent removal of the tumor in the forehead followed by the course of chemotherapy. The third child's disease began as aplastic anemia. And in one patient AML developed as a secondary disease after Hodgkin's disease with inadequate intensive course of chemotherapy and radiotherapy.

Initial clinical symptoms of AL in the majority of observed children were not specific, but their severity significantly determined further course and prognosis of the disease. At the onset of the disease the majority of patients had symptoms of intoxication (94.6 ± 2.3%), that were most evident in boys (p= 0.0000) regardless of the form of leukemia (Tab. 2).

Table 1.

Distribution of AL patients by age at the moment of diagnosis

Syndrome		Total p% ± Sp% (n=92)	ALL p% ± Sp% (n=75)	AML p% ± Sp% (n=17)
Fever		82.6 ± 4.8	81.3 ± 3.4	88.2 ± 7.3
Intoxication		94.6 ± 2.3	90.7 ± 3.7	94.1 ± 6.9
Pain syndrome	osteoarticular	47.8 ± 6.5	48.0 ± 4.2	47,0± 7,2
	abdominal	29.3 ±5.9	29.3 ± 5.6	29,4 ± 6,9
Hemorrhagic syndrome		77.2 ± 5.4	69.3 ± 5.8	88.2 ± 12.0
Hepatolienal syndrome		96.7 ± 2.3	97.3 ± 2.2	94.1 ± 6.9
Lymphadenopathy		84.8 ± 4.7	90.7 ± 3.7	52.9 ± 13.3
Leukocytosis		52.2 ± 6.5	53.3 ± 6.3	52.9 ± 13.3
Anemia		82.6 ± 4.9	89.3 ± 4.02	70.6 ± 12.0
Thrombocytopenia		81.5 ± 5.1	85.3 ± 4.4	94.1 ± 6.9
Increased level of acute phase proteins		90.2 ± 3.9	89.3 ± 3.5	94.1 ± 5.4

Fever was present in 82.6± 4.8% of cases and it was more typical for boys (p= 0.0231). At the time of hospital admission 23.7 ± 4.9% of children were found to have decreased physical development (one or more σ in height and weight) which was more typical in girls (38.5 ± 9.5% in girls

VS 16.0 ± 5.1% in boys; p =0.0172).

Pale skin was observed in almost half of the children (43.4% of children) without a significant difference between the groups. Swelling of the lower extremities, edema of eyelids was observed in small number of patients and it was likely associated with hypoproteinemia.

Ostioarticular pain was reported by 47.8 ± 6.5% of patients and in 23.7% of cases pain in the bones and spine was the main presentation at the onset of the disease, and it was most prevalent in girls (p=0.0045). Pains in the abdomen were observed in 15.3% of cases. A headache was present in 9 children. Cardiac pain was observed in 2 children of older age.

Hemorrhagic syndrome at the onset of the disease was observed in most patients (77.2 ± 5.4%) with a tendency to be more common in AML (p=0.0580) regardless of gender (p=0.0955). Petechiae and ecchymoses on the skin of the upper and lower extremities were detected in 77.2 ± 5.4% of cases. Enanthema on the soft palate was observed in 51.3 ± 5.7% of children. Bleeding of mucous membrane of the oral cavity and nose was less common (in 11.8 ± 3.7% of children).

Lymphoproliferative syndrome was present in most patients. Lymphadenopathy was detected in 84.8 ± 4.7% of children. It was more frequent at lymphoblastic types of AL (p =0.0003) and in boys (p=0.0041). Hepatosplenomegaly was noted in the majority of children (96.7 ± 2.3%), regardless of gender and type of leukemia. Gingival hyperplasia as lymphoproliferative syndrome was observed in 9 cases and enlargement of testes was observed in 6 boys.

Cardiac syndrome at the onset of the disease developed in more than a quarter of cases (26.1%). This syndrome manifested as cardiac pains (in adolescents), dyspnea, arrhythmias, and decreased ejection fraction (less than 60% according to ultrasonography of the heart). Renal syndrome such as changes in urinalysis as leukocyturia, microscopic hematuria, proteinuria, rarely casts in urine manifested in 14.5% of children. Bronchitis or pneumonia was observed in 13.2% of patients. At the onset of the disease intestinal disorders in the form of diarrhea were reported by 9.2% of patients.

At the onset of the disease anemia was a frequent laboratory sign, occurring in 82.6±4.9% of children under investigation. It was more common in girls (p=0.0303). Thrombocytopenia was more common in boys (p=0.0491). Leukocytosis was found in 52.2 ± 6.5 % of patients and it was more common in boys (p=0.044). Leukocytosis more than 200 * 109/l was present in 12.9% of cases. Leukopenia was in 23.7% of patients without noticeable differences in AL type.

Indices of acute phase of inflammation (seromucoid, glycoproteins) increased in all children with AL at the onset of the disease, regardless of age and gender. Hypoproteinemia less than 60 g/L developed in 28.9% of children. Significant differences in levels of crude protein in different groups was not detected.

Discussion

This study shows that early diagnosis (less than 2-3 weeks since the first symptoms) was made just in about half of cases. In our opinion, diagnostic mistakes were probably associated with both variable manifestations and lack of oncological alertness and lack of information awareness of all diagnostic details of AL in children at primary care stage.

Analysis of literature showed that these problems in early diagnosis of AL and other types of cancer for pediatricians and general practitioners are typical not only in our country. Basing on the data of a review made by Dang-Tan T, Franco EL [3] in the developed countries the period from first signs to the diagnosis ranges from 1 day to several months, most typically several weeks.

One of described reasons of diagnostic delay is a relatively low incidence of childhood cancer and other life-threatening conditions [4]. Feltbower R.G., Lewis I.J. et al. [5] note that primary care practitioner sometimes examines a child with a new case of cancer only once in 20 years. According to Danish national population-based study [6] diagnostic interval for a quarter of children with cancer is more than 3 months.

In spite of this, Riccio I, Marcarelli M.[7] showed that musculoskeletal problems in pediatric acute leukemia was observed in 22% of children, this variant of manifestation

most frequently results in diagnostic difficulties [8,9,10].

To understand better the problems in AL diagnosis in children faced by general practitioners, Rachel T Clarke, Caroline HD Jones, Christopher D Mitchell and Matthew J Thompson conducted a study in Southern England with a thorough assessment of 18 pediatric AL cases with diagnostic interval from 5 days to 6 months, including interviews of 18 mothers, 3 fathers and 9 doctors [11]. According to their findings main reasons of diagnostic delay included wrong variety and non-specify of initial symptoms, wrong interpretation of the symptoms by doctors or patient's parents, problems of parent–doctor interaction, a relatively short and defined list of signs in most descriptions of manifestation of childhood leukemia.

4 CONCLUSIONS

Our study showed that lymphoblastic AL is much more typical in children. Among them there is B-type with general prognosis and a rarer T-type with favorable prognosis. Myeloid AL (M0 and M5) with less favorable prognosis and requiring the use of more intensive chemotherapy protocols is a less common pathology. Acute leukemia is more common in boys.

Despite the fact that the disease in the majority of children manifested with intoxication (94.6±2.3%), lymphadenopathy (84.8 ± 4.7%), hepatosplenomegaly (96.7±2.3%), anemic (82.6±4.9%), haemorrhagic (77.2±5.4%) syndromes, only in half of the patients the correct diagnosis was established in the period less than 2-3 weeks since the first symptoms appeared.

In the presence of hemorrhagic syndrome, severe anemia, expressed enlargement of the lymph nodes children were brought under the supervision of a hematologist in time. In other cases, variable and non-specific initial manifestations of AL in children and general practitioners' and specialists' lack of oncologic awareness led to late diagnosis and delayed start of the treatment. All these facts could affect the overall prognosis of the disease.

In conclusion, it should be noted that thorough history taking and comprehensive assessment of clinical symptoms are crucial in the early diagnosis of acute leukemia in children. If a child has symptoms of intoxication, pale skin, lymphadenopathy, hepatosplenomegaly, fatigue, weakness, weight loss, bone pain without any reason, it is necessary to perform a complete blood count test and to monitor blood test parameters over time. It is also necessary to consult a hematologist, especially when the treatment of the disease does not bring any adequate therapeutic effect.

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