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RESEARCH ARTICLE

Incidence of Life-threatening Diseases in Children Referred to the Pediatric Hematology and Oncology Polyclinic

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ABSTRACT

Objective: Direct referral of patients to pediatric hematology and oncology outpatient clinics without questioning their complaints, investigating the etiology, and following up causes concern in patients and families and increases the burden on oncology outpatient clinics. However, very few of these children have conditions that cannot be diagnosed and managed by pediatricians, and even fewer are diagnosed with life-threatening conditions. In this study, we examined the diagnoses of patients admitted to the pediatric hematology and oncology outpatient clinic, the rate of life-threatening diseases, and the need for referral.

Materials and Methods: We retrospectively reviewed the records of patients referred or consulted by pediatricians to the Pediatric Hematology and Oncology Outpatient Clinic over a one year period.

Results: Among the 4210 patients included in the study, the most common diagnosis was anemia, followed by lymphadenopathy, bleeding disorders, and infantile hemangioma. Of these patients, 0.95% (n=40) were diagnosed with life-threatening diseases. Only 0.07% of the patients died during the follow-up period.

Conclusion: This very low life-threatening diseases and mortality for a reference center suggests that patients are referred to pediatric hematology and oncology outpatient clinics without comprehensive evaluation in primary and secondary health care centers.

Keywords: Child, life-threatening diseases, pediatric hematology and oncology

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INTRODUCTION

Pediatrics has a special place in the health sciences. All available resources should be mobilized to ensure that children, the future of societies, grow up as healthy individuals. However, it is necessary to differentiate diseases that require advanced diagnostics from others. Pediatric hematology and oncology outpatient clinics are specialized units that focus on hematological diseases and cancers. Families of patients referred to these clinics are concerned that their child may have a life-threatening condition. Not referring these patients unless there is a real indication will reduce the unnecessary workload in these outpatient clinics, increase the time available for examination and investigation of patients with significant hematologic/oncologic disease, and prevent unnecessary anxiety for families.

The most common reason for presentation to pediatric outpatient clinics is various infections, especially upper respiratory tract infections. Other common causes include anemia, lymphadenopathy and bleeding disorders. These diseases are also among the most common reasons for admission to pediatric hematology and oncology outpatient clinics.

Anemia is a major global health problem affecting children. According to 2001 World Health Organization data, 30% of children aged 0–4 years and 48% of children aged

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5–14 years in developing countries are anemic.[1] Nutritional anemias (iron deficiency anemia, vitamin B12 deficiency anemia, folate deficiency) account for a significant proportion of anemias. Nutritional anemias result from deficiencies of micronutrients essential for hematopoiesis and are clinically defined by the presence of anemia with an inappropriately low reticulocyte count response by the bone marrow for the degree of anemia. They are often grouped by size or mean corpuscular volume, with microcytic anemia most commonly due to iron deficiency anemia and macrocytic or megaloblastic anemia due to either vitamin B12 or folate deficiency. Iron deficiency is the most common nutritional deficiency in children and is prevalent worldwide, affecting 2 billion people, primarily women and children. While patients of any age can be affected, pediatric patients are typically between the ages of 6 months and 3 years or 11 and 17 years because of the rapid growth that occurs during these periods. The prevalence of iron deficiency anemia has been reported to be between 15.2% and 62.5% in various studies conducted in the pediatric age group in Türkiye.[2–4] Megaloblastic anemias result from impaired DNA synthesis in hematopoietic cells and are characterized by macrocytosis with marked variation in erythrocyte size and shape, correspondingly low reticulocyte count, hypersegmented neutrophils, and occasionally pancytopenia. In more than 95% of cases, megaloblastic anemia is the result of folate and vitamin B12 deficiency.[5]

During childhood, lymphatic tissue increases in volume with the maturation of the immune response due to new and frequent antigen exposure. Therefore, the size and number of lymph nodes that begin to form in the prenatal period increase markedly in early childhood. While lymph nodes are rarely palpated in the newborn, they are detected with increasing frequency during infancy. During adolescence, the amount of lymphatic tissue reaches twice that of the adult and from this period, involution of lymphatic tissue begins, as in the thymus and bone marrow.[6,7] In addition to the physiologic volume increase in lymphatic tissue in childhood, lymph node sizes may increase due to many different causes including inflammation, infection, cellular infiltration and foreign matter accumulation in histiocytic cells due to their filtering function. Enlarged lymph nodes in childhood are very common and usually do not require further investigation, but can be concerning for parents and the evaluating physician. Studies have shown that lymph nodes around 1.5 cm can be palpated normally in 27% of infants aged 0–6 months, 52% of children aged 6 months-2 years and 90% of children aged 4–8 years, with no additional complaints or findings.[8] The most common cause of lymphadenopathy in children is infections. Although malignancies are included in the etiology, studies have reported that the probability of malignancy in lymphadenopathies evaluated in primary healthcare institutions is 1%. In pediatric oncology reference centers, this rate is 13–27%.[9,10]

Hemostasis is the body's ability to spontaneously stop bleeding and maintain the fluidity of blood in the vascular system. Hemostasis is achieved when bleeding and clotting are in balance. In normal hemostasis, when bleeding occurs in the body, it is easily stopped, but the clot that forms becomes diffuse and is controlled by the fibrinolytic system. When bleeding occurs, a two-step system is involved; primary hemostasis involves the vessels and platelets, and secondary hemostasis involves the coagulation system. Primary hemostasis is vasoconstriction, platelet adhesion, and platelet aggregation resulting in platelet occlusion and formation of a fibrin clot. In secondary hemostasis, the goal is to form a fibrin clot to form a primary to strengthen the thrombus formed in hemostasis and can easily dissolve. Secondary bleeding disorders in children occur as a result of congenital or acquired coagulation factor deficiencies. Anamnesis, physical examination and laboratory tests are helpful in diagnosis. The presence of gingival bleeding, epistaxis, easy bruising, menorrhagia, hematuria, gastrointestinal bleeding, joint bleeding and bleeding after injury should be questioned.

Infantile hemangioma (IH) is the most common benign vascular tumor of childhood. Infantile hemangiomas occur in approximately 4% of children[11] and usually resolve spontaneously. However, IH can cause permanent disfigurement and functional impairment. To provide the best treatment for infantile hemangiomas, treatment regimens should be selected based on the age of the child, the size and location of the lesion, the presence of complications, the conditions of administration, and the potential outcomes of treatment.

Hemoglobinopathies are the most common monogenic disorders in the world with an ever increasing global disease burden each year.[12] Hemoglobinopathies, especially thalassemia, sickle cell anemia and hereditary spherocytosis, are a major public health problem in our country and around the world. The high number of consanguineous marriages in our country increases the incidence of thalassemia, which is a genetically inherited disease, hundreds of children with the disease are born every year, and families and society suffer material and moral damage. Patients with thalassemia major, hereditary spherocytosis and severe forms of sickle cell disease require regular erythrocyte suspension support to survive.

Polycythemia vera (PV) is characterized by erythrocytosis, leukocytosis, thrombocytosis, splenomegaly, microcirculatory disorders, increased risk of thrombosis, and risk of acute myeloid leukemia. The presence of a JAK2 mutation associated with a hemoglobin level >16.5 g/dL in men or 16 g/dL in women is considered diagnosis. The goal of treatment is to prevent thrombosis.[13]

In our study, we investigated the diagnoses, life-threatening diseases and mortality rates of patients admitted to pediatric hematology and oncology outpatient clinics, which are reference centers.

MATERIALS and METHODS

Pediatric patients aged 0–18 years who presented to the Pediatric Hematology and Oncology outpatient clinic within one year were included in the study. In our country, in order to be examined in the pediatric hematology and oncology outpatient clinic, the pediatrician must first examine and evaluate the patient and, if deemed necessary, approve the referral to us through the official electronic system. Therefore, all patients who applied to our outpatient clinic were examined by a pediatrician. The presenting complaints, physical examination findings, laboratory results, diagnoses, treatments, life-threatening diseases and mortality rates were retrospectively evaluated from the patient files. Patients with the same diagnosis were divided into groups and these patients were analyzed in terms of life-threatening diseases and mortality rates within their own groups.

Hemoglobin concentration cut-offs are established by the World Health Organization (WHO) for major populations; however, ethnicity, gender, sex, and pathophysiologic status may alter these criteria:[14] 6 months to 4 years of age: Hb <11.0 g/dL, 5 to 11 years of age: Hb <11.5 g/dL, 12–14 years: Hb <12.0 g/dL, >15 years: men Hb <13.5 g/dL, women Hb <12 g/dL, patients with vitamin B12 levels less than 200 pg/mL were considered to have vitamin B12 deficiency and patients with folate levels less than 3 ng/mL ng/mL were considered to have folate deficiency.[15] Patients with one or more of these anemias were included in the "nutritional anemia" group.

Patients with lymphadenopathy meeting the criteria for pathologic lymphadenopathy were referred to pediatric surgery for excisional biopsy. Lymphadenopathies larger than 1.5 cm in diameter in the inguinal, axillary, and femoral regions or 3 cm in diameter in the cervical region, located in the supraclavicular region, and fixed after 2 weeks of antibiotic treatment were considered pathologic lymph nodes.[16]

Blood factor levels were obtained from patients with bleeding or abnormal coagulation tests. Patients with factor levels below 50 IU on two separate measurements were diagnosed with factor deficiency, and factor replacement was initiated in patients with severe bleeding episodes.[5]

Hemoglobin electrophoresis was ordered in patients admitted with a prior diagnosis of thalassemia carrier. Patients with a hemoglobin A2 level greater than 3.5 were considered thalassemia carriers. Patients with a hemoglobin level below 8 g/dl were referred for thalassemia genetic testing, the diagnosis of thalassemia major was confirmed, and erythrocyte suspension support was initiated.[5]

Patients with elevated hemoglobin levels were evaluated for PV and interviewed about neurologic and respiratory symptoms, family history, and history of thrombosis. Patients with hemoglobin levels above 16.5 g/dL in boys and 16 g/dL in girls were followed up.[13]

Life-threatening disease assessment was performed according to the following criteria:

- Patients with a hemoglobin value <4 mg/dL and concomitant evidence of cardiac dysfunction who are on erythrocyte suspension support.
- Patients diagnosed with cancer after histopathologic examination of lymph node excisional biopsy specimen with pathology report as lymphoma
- Patients diagnosed with acute leukemia by Flow Cytometry in patients with bicytopenia/pancytopenia or hyperleukocytosis.
- Patients with bleeding and rapidly decreasing hemoglobin levels who are receiving fresh frozen plasma or factor concentrates to control bleeding.
- İnfantile hemangiomas with ulceration and infection extending into deeper layers of the skin.
- Patients with hemoglobinopathy who require regular erythrocyte suspension support.
- Patients presenting with elevated hemoglobin levels and diagnosed with PV with elevated levels in other blood series, history of thrombosis or JAK-2 mutation.
- Patients with cancer diagnosis and initiation of chemotherapy treatment.

Applications of patients who came to get the results of the tests were excluded from the study.

All procedures were approved by the Bakırkoy Dr. Sadi Konuk Training and Research Hospital Ethics Committee (Date:

Table 1. Disease frequencies

	n	%
Anemia	858	20
Prediagnosis of anemia without anemia	243	5.8
Lymphadenopathy	759	18
Bleeding	533	12.6
Infantile hemangioma	405	9.6
Prediagnosis of thalassemia carrier	255	6
High hemoglobin levels	115	2.7
Thrombocytopenia	234	5.5
Liver/spleen diseases	108	2.56
Hemolytic anemia	72	1.7
Arteriovenous malformations	63	1.5
High vitamin B12 levels	52	1.2
Other	693	

June 24, 2024, No:2024-04-03). The study was conducted in accordance with the tenets of the Declaration of Helsinki.

Statistical Analysis

Data analysis was performed using Statistical Packages for Social Sciences version 25 (IBM Inc., Armonk, NY, USA), and descriptive statistical results are presented.

RESULTS

4210 patients were included in the study. The most common presenting diagnoses were anemia (20%), lymphadenopathy (18%), bleeding disorders (12.6%) and hemangioma (9.6%) (Table 1).

The most common reason for presentation to the pediatric hematology outpatient clinic was anemia. Nutritional anemia was detected in a total of 858 (20%) patients; although 243 (5.8%) patients were referred with a prediagnosis of anemia, anemia was not detected in these patients. Only 8 of the patients who were referred as not responding to anemia treatment required IV iron supplementation. Three (0.07%) of the patients with anemia had a hemoglobin level below 5 g/dL and associated signs of cardiac dysfunction. These patients received erytrosit suspension support and were considered life-threatening. No patients died from anemia.

Seven hundred fifty-nine patients applied with the complaint of lymphadenopathy. Excisional lymph node biopsy was performed in 11 of 13 patients who met pathological lymph node criteria; the diagnoses were reactive hyperplasia (n=5), granulomatous lymphadenitis (n=1), Hodgkin's lymphoma (n=4) and giant cell fibrohistiocytic tumor (n=1). Two patients were diagnosed with acute lymphoblastic leukemia. In total, malignant etiology was detected in only 6 patients with lymphadenopathy and life-threatening disease was accepted. No patient died.

Five hundred thirty-three patients presented with bleeding (epistaxis, menorrhagia, circumcision bleeding, umbilical bleeding, intracranial bleeding) and easy bruising. Seventy-five patients presented with prolonged coagulation tests. A total of 8 patients, including one patient with hemophilia A, two patients with factor X deficiency, four patients with von Willebrand disease, and one patient with combined deficiency of vitamin K-related factors, were diagnosed with life-threatening disease, treated with factor concentrates, and started on prophylaxis; none of these patients died.

The fourth most common reason for presentation was infantile hemangioma. A total of 405 patients were admitted for IH. None of these patients developed loss of function or severe life-threatening bleeding/infection due to infantile hemangioma.

Of 255 patients with a prediagnosis of thalassemia carrier, 148 were diagnosed as thalassemia carrier, 3 as thalassemia major, 3 as alpha thalassemia, 3 as sickle cell anemia, and 5 as hereditary spherocytosis. Of these patients, 93 were not diagnosed with hemoglobinopathy and were referred with an incorrect prediagnosis. Three patients diagnosed with thalassemia major received regular erythrocyte suspension support at intervals of three to four weeks; these 3 patients were included in the life-threatening disease group.

None of the 115 patients with elevated hemoglobin levels and a prediagnosis of PV had life-threatening neurological or respiratory symptoms or thrombosis.

Apart from these patients, 234 of 4210 patients had thrombocytopenia; 153 had elevated/low blood count series; 108 had hepatomegaly, splenomegaly, hepatosplenomegaly, cyst in the liver, cyst in the spleen; 72 had hemolytic anemia; 63 had arteriovenous malformations; 63 patients were referred to the Pediatric Hematology and Oncology Outpatient Clinic because of wrong outpatient appointment; 52 patients had high vitamin B12 levels; and the remaining patients were referred to the Pediatric Hematology and Oncology Outpatient Clinic for suspected cancer, thrombosis, personal history of cancer, request for investigations, mastocytosis, neurofibromatosis, blood group determination, and other reasons. Among these patients, 14 patients were diagnosed with cancer, including 11 acute lymphoblastic leukemia (ALL), 1 Burkitt lymphoma, 2 Langerhans cell histiocytosis, and 3 of these patients died. In this group of patients, 1 patient was

Table 2. Life-threatening diseases and death

	Life-threatening disease	Dead
Anemia	3	0
Lymphomas	7	1
Congenital factor deficiency	8	0
Thalassemia major	3	0
Acute leukemia	14	2
Chronic immune thrombocytopenic purpura	3	0
Langerhans cell histiocytosis	2	0
Total	40	3

diagnosed with severe aplastic anemia (transfusion-dependent) and 3 patients were diagnosed with chronic immune thrombocytopenic purpura with bleeding disorders.

Including 3 lymphomas and 2 ALL diagnosed in patients with lymphadenopathy, a total of 19 children were diagnosed with cancer among 4210 patients, and 3 patients died (Table 2).

DISCUSSION

In our country, the family doctor does not need to refer patients to a pediatrician in order to make an appointment for a pediatric outpatient clinic. Patients can make an appointment directly with a pediatrician online or by phone. This may have caused pediatricians to act like primary care physicians over time, referring a large proportion of patients to subspecialty outpatient clinics. These subspeciality outpatient clinics are located in training and research hospitals and university hospitals. In the last year, 4210 patients were admitted to our Pediatric Hematology and Oncology outpatient clinic. Only 0.95% of these patients were diagnosed with life-threatening diseases. The mortality rate is very low in terms of 0.07%. Our study was conducted in a teaching and research hospital, but different results might have been obtained if it had been conducted in a university hospital. Although the choice between the two hospitals is up to the patient, the small number of university hospitals compared to training and research hospitals and the high likelihood that pediatricians refer patients directly to university hospitals for conditions with a high mortality risk may play a role in this difference.

Each year, 429,000 children and adolescents are expected to develop cancer. One study reported a five-year survival rate of up to 80 percent for 45,000 children with cancer in high-income countries, compared with less than 30 percent for 384,000 children in low- and middle-income countries.[17] Geographical and ethnic differences in age-specific incidence rates exist. Understanding why children die is necessary to implement strategies to prevent future deaths and improve the health of any community. Although there are fewer pediatric hematology and oncology specialists in our country compared to developed countries, most of the referrals may be unnecessary, as seen in our study. This situation further increases the workload of pediatric hematology and oncology specialists. Considering the lower survival rates in our country compared to developed countries, it is even more important to refer only life-threatening diseases to pediatric hematology and oncology outpatient clinics. Paying more attention to the patient's follow-up and treatment process and spending more time on it can increase survival rates.

It has been observed that the majority of anemias, which are the most common reason for referral, can be managed by pediatricians and respond to drug treatment. Percentage of patients referred for anemia was 22% who were not anemic. Only 8 of these patients were resistant to iron treatment and received intravenous iron treatment. The number of patients who developed heart failure and received erythrocyte suspension support is only 3. Children with anemia can be followed up in pediatric outpatient clinics if appropriate and adequate doses of medication are initiated and if they are provided with regular and correct use of the medication. The number of patients presenting with lymphadenopathy (n=759) is quite high. Only 6 of these patients were diagnosed with cancer and started chemotherapy. It has been observed that the majority of patients referred by pediatricians do not even meet the pathological lymph node criteria. Ultrasonography (USG) was performed in all patients with LAP prior to referral to the pediatric oncology outpatient clinic. However, USG is an operator-dependent imaging method and is not sufficient to differentiate pathologic lymph nodes on its own. As a matter of fact, in our study, benign LAP was detected in the majority of patients who were described as pathologic LAP on USG.

Because patients in our country can make appointments directly with specialists, many patients who can be diagnosed and treated in primary care are referred to the main branch outpatient clinics. Due to the number of examinations, which can reach up to 100 patients per day in the main branch outpatient clinics, doctors may be worried about completing these examinations in a short time, and this may be the reason why these patients are referred to the subspecialty outpatient clinics without sufficient questioning. Some families demand that their children be seen by an oncologist to make sure they do not have a serious illness. These demands can put pressure on the physician.

Considering the small number of hematology-oncology specialists (about 350 in Türkiye), it does not seem right to refer a patient to an oncologist without further tests. For many reasons, pediatric health and disease clinics sometimes function as outpatient clinics that refer patients to various subspecialties. Accurate clinical and laboratory evaluation of patients for systemic signs and symptoms will reduce unnecessary referrals. In this way, it may be possible to prevent the anxiety that patients experience when they come to the oncology outpatient clinic.

CONCLUSION

In conclusion, only 0.95% of our patients were diagnosed with life-threatening diseases. The number of patients diagnosed with cancer and started chemotherapy treatment constituted 0.5% of all patients. These rates are quite low for an oncology center. It was observed that patients who could mostly be followed up in primary or secondary health care centers were referred to the oncology outpatient clinic.

Disclosures

Ethics Committee Approval: The study was approved by the Bakırköy Dr. Sadi Konuk Training and Research Hospital Non-interventional Scientific Research Ethics Committee (No: 2024-04-03, Date: 24/06/2024).

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