Evaluation of Etiological Factors Causing Hypereosinophilia in Children

Çocuklarda Hipereozinofiliye Neden Olan Etiyolojik Faktörlerin Değerlendirilmesi

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ABSTRACT

Objective: Patients with persistent eosinophilia may have many conditions ranging from relatively benign diseases such as parasitic serious infections to life-threatening serious diseases. We aimed to determine the etiological causes of hypereosinophilia in children.

Material and Methods: Patients under 18 years of age who had complete blood counts in Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital's pediatric clinics between January 2013-January 2016 were retrospectively analyzed. Hypereosinophilia was defined as having at least two peripheral blood absolute eosinophil counts greater than or equal to 1500/mm^3.The results of the examinations and diagnoses when the patients were detected with hypereosinophilia were recorded from the hospital records.

Results: Three hundred and forty patients who underwent complete blood count were found to have hypereosinophilia. Seventy patients whose file records could not be accessed were excluded from the study. Two-hundred seventy patients (56% male) with a median age of 5 (IQR:1-12) years were included in our study. When the diagnoses of patients were examined, 48 (17.8%) had allergic diseases, 21 (7.8%) had immunodeficiency, 14 (5.2%) had parasitic disease. 15 (5.5%) had tumor, 4 (1.5%) had leukemia, 2 (0.7%) had hypereosinophilic syndrome, 2 (0.7%) had adrenal insufficiency

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and 2 (0.7%) had burn. Ninety-nine (36.7%) patients were found to use medication for any disease (acute or chronic). As a result of the examinations performed in 63 (23.3%) patients, it was found that there was no reason to explain hypereosinophilia.

Conclusion: The number of eosinophils may increase in many conditions. The cause of increase in eosinophil may not always be found. Further studies are needed on the long-term prognosis of these patients.

Key Words: Allergic diseases, Childhood, Hypereosinophilia, Immunologic diseases, Parasitic infections

ÖZ

Amaç: Hipereozinofili hastaları, paraziter enfeksiyonlar gibi nispeten iyi huylu hastalıklardan yaşamı tehdit eden ciddi hastalıklara kadar pek çok duruma sahip olabilir. Çalışmamızda çocuklarda hipereozinofilinin etiyolojik nedenlerinin belirlenmesi amaçlanmıştır.

Gereç ve Yöntemler: Ankara Çocuk Sağlığı ve Hastalıkları Hematoloji Onkoloji Eğitim ve Araştırma Hastanesi pediatri kliniklerinde Ocak 2013 - Ocak 2016 tarihleri arasında tam kan sayımı yapılan 18 yaş altı hastalar retrospektif olarak incelendi.

En az iki tam kan sayımı ölçümünde periferik kan mutlak eozinofil sayısının 1500/mm^3 veya daha büyük olması hipereozinofili olaral kabul edildi. Hastane kayıtlarından hipereozinofili tespit edildiğinde yapılan tetkik ve tanıların sonuçları kaydedildi.

Bulgular: Tam kan sayımı yapılan çocuk hastaların 340'ında hipereozinofili olduğu tespit edildi. Dosya kayıtlarına ulaşılamayan 70 hasta çalışma dışı bırakıldı. Çalışmamıza, yaşları ortanca 5 (1-12) [ortanca (çeyrekler arası aralık (ÇAA)] yıl olan 270 (%56'sı erkek) hasta dahil edildi. Hastalara konulan tanılar incelendiğinde: 48'ine (%17.8) alerjik hastalık, 21'ine (%7.8) immün yetmezlik, 14'üne (%5.2) paraziter hastalık, 15'ine tümör (%5.6), 4'üne (%1.5) lösemi, 2'sine (%0.7) hipereozinofilik sendrom, 2'sine (%0.7) adrenal yetmezlik, 2'sine (%0.7) yanık tanısı konulduğu tespit edildi. Doksan dokuz (%36.7) hastada ise herhangi bir hastalık için (akut veya kronik) ilaç kullanımı (antibiyotik, antiepileptik, demir şelatörü gibi) olduğu tespit edildi. Altmış üç (%23.3) hastada ise yapılan tetkikler sonucunda hipereozinofiliyi açıklayacak bir neden bulunamadığı görüldü.

Sonuç: Kanda eozinofil sayısı pek çok durumda da yükselebilir. Eozinofil yüksekliğinin sebebi her zaman bulunamayabilir. Bu hastaların uzun dönem prognozları hakkında yapılacak ileri çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: Alerjik hastalıklar, Çocukluk çağı, Hipereozinofili, İmmünolojik hastalıklar, Paraziter enfeksiyonlar

INTRODUCTION

Eosinophils are bone marrow-derived peripheral blood and tissue granulocytes with important roles in host defense and allergic inflammatory response. Peripheral blood eosinophilia is defined as an increase in absolute eosinophil counts (AECs) above the upper reference limit (1,2).

Many clinical conditions can increase the blood eosinophil level by stimulating eosinophilopoiesis in the bone marrow. Polyclonal eosinophil proliferation can occur in response to overproduction of IL-5. The sources of IL-5 secretion in an amount that can induce eosinophilia are type-2 cytokine-producing T cells (CD4 helper T cells), malignant cells (solid tumors such as adenocarcinoma) and lymphomas, especially in response to parasitic helminthic infections and allergens (3).

The peripheral blood eosinophil count greater than 500 Eo / microL is defined as eosinophilia (4). The term hypereosinophilia is used to describe moderate and severe eosinophilia (> 1500 Eo / microL) (5).

Hypereosinophilia is defined as an eosinophil count above 1500 Eo / microL, which is measured at least 2 times with an interval of at least 4 weeks (6). Patients with persistent eosinophilia may have many conditions ranging from relatively benign diseases such as parasitic serious infections to life-threatening serious diseases (7). Persistent eosinophilia should prompt additional clinical evaluation. Studies evaluating the etiology of hypereosinophilia in children are fewer compared to adults, and the underlying causes of hypereosinophilia are not well known in pediatric patients as in adults (8).

To treat hypereosinophilia, it is important to find the condition that causes hypereosinophilia. In our study, it was aimed to determine the clinical features and etiological factors of hypereosinophilia in pediatric patients

MATERILAS and METHODS

Patients under 18 years of age who had complete blood counts in Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital's pediatric clinics between January 2013 and January 2016 were retrospectively analyzed. Patients with hypereosinophilia were included in the study. Hypereosinophilia was defined as an eosinophil count above 1500 Eo / microL, which is measured at least 2 times with an interval of at least 4 weeks.

The study was approved by the Clinical Research Ethics Committee of Ankara Pediatric Hematology and Oncology Research and Training Hospital (27.03.2021/2017-016).

To obtain complete blood count (CBC), peripheral blood was collected in an EDTA vacutainer tube and analyzed by an autoanalyzer (LH780 (Beckman Coulter, USA.)

Demographic characteristics of patients such as gender, age at diagnosis, personeal and family history of allergic and chronic disease, symptoms and physical examination results

Table I: The characteristics of the study patients.

Age at onset of hypereosinophilia (year) Median (IQR)	5 (1-12)
Sex, n (%) Male Female	152 (56.2) 118 (43.8)
History of chronic illness, n (%)	154 (57)
Consanguinity, n (%)	59 (21.8)
Total IgE (kU/L) Median (IQR)	426 (166-922)
Eosinophil count at diagnosis (/mm³) Median (IQR)	1800 (1600-2300)
Eosinophil persentage at diagnosis (%) Median (IQR)	14.9 (10.9-19.6)

were recorded (Table I). Laboratory data were also recorded, when available. Parameters previously shown or suspected to have prognostic significance in HES were recorded, when available, including peak eosinophil count, serum tryptase, serum IgE level, vitamin B12 level, Parameters included in the initial diagnostic workup for hypereosinophilia were recorded, when available, such as liver and kidney function tests allergy test results such us skin prick test and serum specific IgE level and stool/serology for parasites. Also tests to evaluate for end-organ involvement and/or tissue eosinophilia (such as computed tomography of the chest, abdomen, and pelvis; electrocardiogram;echocardiogram; pulmonary function test; and pathology from bone marrow, gastrointestinal tract, lung, and/or liver) were reviewed, when available.

Statistical Methods:

Statistical analyses were performed using the SPSS 22 (IBM Corporation, Armonk, NY. Numbers and percentages are reported for discrete variables and means and standard deviations for continuous variables. Values are presented as means and standard deviations for data demonstrating a normal distribution and as medians and interquartile ranges (IQR) for data not demonstrating a normal distribution.

RESULTS

During the study period, 340 patients who underwent CBC were found to have hypereosinophilia.

File records of 270 of these patients were reached. Seventy patients whose file records could not be accessed were excluded from the study.

Two-hundred seventy patients (56% male) with a median age of 5 (IQR: 1-12) years were included in our study. When the diagnoses of patients at the time of hypereosinophilia were examined, 48 (17.8%) had allergic diseases, 21 (7.8%) had immunodeficiency, 14 (5.2%) had parasitic disease.

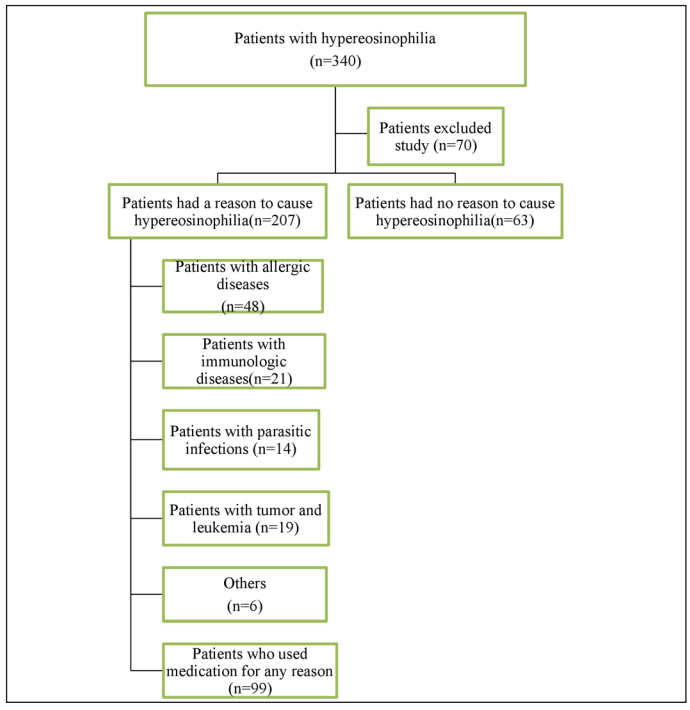

Figure 1: Diagnosis of patients with hypereosinophilia.

15 (5.6%) had tumor, 4 (1.5%) had leukemia, 2 (0.7%) had hypereosinophilic syndrome, 2 (0.7%) had adrenal insufficiency and 2 (0.7%) had burn. Ninety-nine (36.7%) patients were found to use medication for any disease (acute or chronic).

As a result of the examinations performed in 63 (23.3%) patients, it was found that there was no reason to explain hypereosinophilia (Figure1).

Patients with allergic disease:

Underlying allergic diseases were detected in 48 (17.8%) patients with a mean age of 4 years (IQR: 1-9). Of the patients, 36 (80%) were male and the median serum total IgE value was 604 kU/L (IQR: 165-852). Of these patients, 13 had asthma, 10 had atopic dermatitis, 16 had food allergy, one had eosinophilic esophagitis, one had house dust mite sensitivity, two had pollen sensitivity, one had contact dermatitis, two had DRESS (drug rash with eosinophilia and systemic symptoms), one had lichenoid drug eruption and one has Steven Johnson Syndrome.

Patients with immunodeficiency:

Immunodeficiency was detected in 21 (7.8%) patients. Four of these patients were followed up for dedicator of cytokinesis 8 (DOCK-8) deficiency, three for chronic granulomatous disease, one for Wiscott-Aldrich syndrome, two for cyclic neutropenia, one for Omenn Syndrome, one for NEMO defect, two for agammaglobunemia, four for Common Variable Immune Deficiency, one for Partial IgA deficiency, one for transient hypogammaglobulinemia of infancy, and one for Kostman Syndrome.

Patients with parasitic disease: Parasitic infection was detected in 14 patients (5.2%). In nine of these patients, there was Echinococcus granulosus, two had *Entamoeba histolytica*, one had *Toxocara*, one had *Fasciola hepatica*, one had *Enterobius vermicularis* infection.

Patients with malignant or benign tumor: Fifteen patients had a malignant or benign tumor. Three of these patients had langerhans cell histiocytosis, two had rhabdomysarcoma, one had rhabdomyoma, one had teratoma, one had hemangioma, one had pilocytic astrocytoma, one had cystic hygroma, one had neuroblastoma, one had mixed germ cell tumor, one had hepatoblastoma, one had non-hodgkin lymphoma, one had congenital cystic hygroma.

Ninety-nine (36.6%) patients were found to use medication for any disease (acute or chronic). Forty-four (16.2%) patients were using antiepileptic (single or multiple combinations of valproic acid, carbamazepine, phenobarbital, phenytoin, clobazam, levetiracetam, topiramate), seven (2.6%) iron chelator (deferasirox), five (1.85%) iron replacement therapy, 35 (13%) antibiotics (single or multiple combinations of meropenem, teicoplanin, ampicillin sulbactam, benzathine penicillin, piperacillin tazobactam, amikacin, amoxicillin clavulanate), one fluoxetine, two patients levothyroxine sodium, one ursodeoxycholic acid, one palivizumab, two granulocyte colony-stimulating factor (GSCF) (donors for hematopoietic stem cell transplantation).

DISCUSSION

In our study, in which we investigated the causes of hypereosinophilia in pediatric patients, while a cause was shown in 40% of the patients, no cause was found in 23.3%, and the remaining 36.7% were found to have no cause other than drug use.

Publications on hypereosinophilia in children are limited in number, mostly in the form of studies and case reports involving a low number of patients (8-14). Burris et al.(9) evaluated pediatric patients with hypereosinophilia and reported that the most common causes of hypereosinophilia were atopic dermatitis, graft-versus-host disease, sickle cell disease and parasitic infections. In addition, they found that there was no reason to explain hypereosinophilia in 34.1% of their patients (9). The most common causes identified in our study were allergic disease (17.8%), immunodeficiency (7.7%), parasitic disease (5.1%), tumor (5.5%), leukemia (1.5%), hypereosinophilic syndrome (0.7%), adrenal insufficiency (0.7%), and burn (0.7%). Approximately one third of our patients were using medication for any reason, and there was no additional disease to explain hypereosinophilia except for drug use, whereas 23.3% drug. This supports that in some cases of pediatric hypereosinophilia, an underlying cause may not be found, as reported by Burris et al. (9) in their study.

In the study conducted by Burris et al.(9), the median age at diagnosis of hypereosinophilia was 4.6 years.

The median age of diagnosis in our study was 5 years, which was consistent with the study of Burris et al.(9).

Although it is known that an increase in the number of eosinophils in the peripheral blood is seen in many conditions such as infectious diseases, malignant or allergic diseases, it has been stated that the most common cause of eosinophilia in the world is parasitic infections. It is reported that parasitic diseases, which are the most common causes of eosinophilia, are echinococcus, strongyloidiasis, schistosomiasis, filariasis, trichinosis, toxocariasis and fasciolosis (15). Williams et al.(8) reported that parasitic diseases in both children and adults were the most common cause of secondary hypereosinophilia in their study with 291 patients with hypereosinophilia, 37 of whom were children. They found that a total of three pediatric patients had parasitic infections and all three were *Toxocara* (visceral larva migrans) infection. In our study, in patients with hypereosinophilia, parasitic infections were the 4th among the detected reasons, nine of our patients had *Echinococcus granulosus*, two had *Entamoeba histolytica*, one had *Toxocara*, one had *Fasciola hepatica*, and one had *Enterobius vermicularis*. *Echinococcus granulosus* is a parasitic disease commonly encountered in the world. Hydatid cyst is endemic in Mediterranean and Middle Eastern countries, including our country (16). We think that in patients with eosinophilia, the frequency of parasitic disease and the type of parasite causing it may vary according to the population in which the study was conducted.

In our study, the most common cause of hypereosinophilia was allergic diseases, and these were asthma, atopic dermatitis, food allergy, pollen sensitivity, eosinophilic esophagitis, house dust mite sensitivity, contact dermatitis, DRESS, lichenoid drug eruption, Steven Johnson Syndrome, respectively. Burris et al. (9) reported in their study with 172 pediatric patients that the most common cause of secondary hypereosinophilia was atopic dermatitis (22 patients). In addition, they reported that five of the patients with secondary hypereosinophilia had asthma (9). In our study, the most common cause of hypereosinophilia was allergic diseases. However, in our study, unlike Burris et al.'s (9) study, the frequency of asthma was higher than atopic dermatitis.

Among the primary immunodeficiencies, Omenn Syndrome, Hyper IgE syndrome and Wiscott Aldrich syndrome may cause eosinophil elevation (17-19). In the study of Burris et al. (9) in which they evaluated 176 pediatric patients with hypereosinophilia, reported that four of their patients had immunodeficiency [Wiskott-Aldrich syndrome in two, Omenn syndrome in one, and

DOCK8 deficiency in one]. When Williams et al. (8) compared pediatric and adult patients with hypereosinophilia, they found that the frequency of immunodeficiency in children was higher than in adults. They also reported that 2 of 37 pediatric patients had immunodeficiency and that they were DOCK8 deficiency and X-linked lymphoproliferative disease. In our study, immunodeficiency was detected in 7.7% of our patients. Four of these patients were followed up due to DOCK8 deficiency, three due to chronic granulomatous disease, one due to Wiscott-aldrich syndrome, two due to cyclic neutropenia, one due to Omenn syndrome, one due to NEMO defect, two due to agammaglobunemia, four due to Common Variable Immune Deficiency, one due to Partial IgA deficiency, one due to transient hypogammaglobulemia of infants, one due to Kostmann syndrome. In immunocompromised patients, eosinophilia can be caused by a variety of processes, including Th1 / Th2 imbalances, cytokine irregularities, infections, and medications (20). We also think that the hypereosinophilia seen in some of our patients is due to the nature of the immunodeficiency they have, while others may have occurred as a result of concomitant infections. While the incidence of primer immunodeficiencies has been reported as 1/1200 in the United States, it has been reported as 30.5/100000 in a study conducted in our country (21,22). The frequency of rare immune deficiencies in our study was 7.7%. This shows that the frequency of immunodeficiency is higher in patients with hypereosinophilia and the diagnosis of immunodeficiency should be kept in mind in these patients.

DRESS (drug rash with eosinophilia and systemic symptoms) is a drug hypersensitivity reaction characterized by fever, diffuse mucocutaneous rash, facial edema, lymphadenopathy (LAP), eosinophilia and/or other hematological abnormalities and visceral dysfunctions (21). In our study, two of our patients also had DRESS. However, in 99 of our patients, there was no other condition to explain hypereosinophilia except drug use. Most of our patients had to continue their medication. Therefore, to confirm that the hypereosinophilia in the patients was due to the drugs, it could not be shown that the drug was discontinued and the eosinophilia recovered. Our results show that patients using drugs can only have eosinophilia without DRESS. Therefore, we think that drug use should be questioned in patients with hypereosinophilia in children.

Despite the large number of patients in our study, there are some limitations. First, because it is a retrospective study, patients were not evaluated with a specific protocol. Secondly, because our patients did not have long-term follow-up information, we could not evaluate the course of hyperosinophilia and organ complications in these patients. Additionally, as a result of the examinations performed in 23.3% of our patients, it was found that there was no reason to explain hypereosinophilia. There may not always be a causal relationship between hypereosinophilia and the clinical conditions reported in patient

As a result,the number of eosinophils may increase in allergic diseases as well as in many conditions other than allergic diseases. The cause of increase in eosinophil may not always be found. Further studies in which these patients are monitored prospectively and provide information about their long-term prognosis are needed.

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