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An Analysis of Diseases Associated with Eosinophilia in Childhood[1]

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= Abstract = We analyzed 500 children who had eosinophils comprising more than 6% of the circulating leukocytes in their blood and more than 250 eosinophils per cubic millimeter for the causal diseases of or the conditions associated with eosinophilia.

Eosinophilia was mainly observed in patients with drug reactions (105 cases), allergic diseases (78 caes) or malignant diseases (60 cases). Drug reactions were caused by penicillin analogues (76 cases) or anti-convulsants, especially carbamazepine (29 cases). Allergic diseases included asthma (36 cases), allergic rhinitis (25 cases), brain tumors (8 cases), non-Hodgkin's lymphomas (7 cases), Hodgkin's diseases (3 cases), acute myeloblastic leukemia (2 cases) or sarcoma (15 cases).

Eosinophils comprising more than 20% of the circulating leukocytes were mainly observed in patients with allergic diseases (38%), malignant disseases (19%) or durg reactions (13%).

It can be concluded that eosinophilia in childhood is mainly associated with allergic diseases, malignant diseases or drug reactions, and of these three causes drug reaction is the most frequent one.

Key words: ***Eosinophilia***

INTRODUCTION

The eosinophilic leukocyte was discovered by Paul Ehrlich in 1879 when he stained fixed blood smears with aniline dyes. The eosinophil is similar in size to the neutrophil and usually contains a bi-lobed nucleus and large cytoplasmic granules containing basic proteins that stain with acidic dyes. The life cycle of eosinophils may be divided into marrow, blood and tissue phases. Eosinophils develop in the bone marrow from precursors that have a common lineage with neutrophils and basophils and also mature in the marrow. They enter the blood and circulate only a few hours before migrating into the tissues, probably by diapedesis at endothelial intercellular junctions. The ratio of tissue and marrow eosinophil to blood eosinophil is 200 : 1 in humans. Thus, eosinophils in the peripheral circulation represent only a small fraction of the total number of eosinophils in the body, and eosinophils in the peripheral circulation are considered to merely "pass through" the circulation en route to the tissue. The majority of eosinophils in the tissues do not recirculate (Jandl, 1987; Slifman *et al.*, 1988).

It was not until the 1970s that the functions of eosinophils were revealed. Two major functions are proposed. The first is as an effector cell for killing helminths. It can induce antibody-dependent or complement-dependent damage to the larval tissue stages of some helminth parasites, such as S. mansoni and Trichinella spiralis. Eosinophils are phagocytic and bactericidal in vitro, but the extent to which they kill the bacteria in vivo is not certain. The second important func-

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tion is their capacity for dampening self-destructive hypersensitivity and inflammatory reactions. They inactivate mediators released from mast cells and remove allergic antigen-antibody complexes by phagocytosis, modulating or dampening reactions associated with IgE-mediated degranulation of the mast cells (Butterworth & David 1981; Weller 1984).

Eosinophils normally comprise about 1-3% of the circulating leukocytes. There is a marked diurnal variation in the level of circulating eosinophils, with the highest level occurring late at night and the lowest in the morning. Eosinopenia is found in hyperadrenalism or shock and is induced by injections of glucocorticosteriod, ACTH or epinephrine. In the early works on eosinophils many investigators reported the association of eosinophilia with helminth infection and allergic diseases. Later eosinophilia was noted in many clinical conditions (Stickney & Heck 1944; Luknes 1972). However, the role of eosinophils in these clinical entities is poorly understood. We attempted to discover the causal diseases of or the conditions associated with eosinophilia and their incidences in childhood.

MATERIALS AND METHODS

Of all the patients seen at the Seoul National University Children's Hospital between September 1988 and February 1989, 500 children who had eosinophils comprising more than 6% of the circulating leukocytes and more than 250 per cubic millimeter were analyzed for the causal diseases of or the conditions associated with blood eosinophilia, and observed for the incidences of causal diseases which were listed by Lukens (1972), Wintrobe (1981), Williams (1983), Weller (1984) and Boldt (1987).

The relative number of eosinophils in the blood was determined by the differential white blood cell count, and the eosinophil count was determined by multiplying the white blood cell count by the % of eosinophils in the differential. The white blood cell count was obtained by using ELT-1500 counter.

RESULTS

Five hundred children who had eosinophils comprising more than 6% of the circulating leukocytes were analyzed for the causal diseases of blood eosinophilia and for their incidences. In this study the incidence of causal diseases which were listed by Lukens (1972), Wintrobe (1981), Williams (1983), Weller (1984) and Boldt (1987) were observed.

Table 1 shows the diseases or conditions showing blood eosinophilia. Of 500 children, eosinophilia was mainly observed in patients with drug reactions (105 cases), with allergic diseases (78 cases), malignant diseases (60 cases) or infectious diseases (12 cases). Infants less than three months old (physiologic eosinophilia), patients with hematologic diseases or with collagen diseses showed eosionphilia in 17 cases, 8 cases or 7 cases, respectively. In allergic diseases, eosionophilia was mainly observed in patients with asthma (36 cases) or allergic rhinitis (25 cases). In malignant diseases, acute lymphoblastic leukemia (25 cases), non-Hodgkin's lymphoma (8 cases), brain tumor (7 cases) or sarcoma (15 cases) accompanied eosinophilia. Infectious disease showing eosinophilia included tuberculosis (5 cases), streptococcal infection (3 cases) and pneumonia (2 cases). Drugs associated with eosinophilia were penicillin analogues (76 cases) or carbamazepine (29 cases).Eosinophilia was also observed in patients with congenital heart diseases (22 cases) or chronic renal diseases (10 cases). Of 500 children, 173 had eosinophilia associated with diseases or conditions that were not included in Williams' list, and Table 2 shows conditions associated with their eosinophilia, including hypertrophy of the tonsils and adenoids (20 cases), strabismus (13 cases), inguinal hernia (7 cases), cleft palate (5 cases), mucocutaneous lymph node syndrome (5 cases). In 94 cases the incidence of conditions associated with their eosinophilia was less than two cases, so that they were classified as others.

The percentage distribution of diseases in association with various degrees of eosinophilia is shown in Table 3. Of the children with eosinophil counts of 6 to 10%, 36% received drugs, 21% had allergic diseases and 16% had malignant diseases. Of the children with eosinophil counts of 11 to 20%, 28% received drugs, 28% had allergic diseases and 24% had malignant diseases. Of children with eosinophil counts of over 20%, 38% had allergic diseases, 19% had malignant diseases and 13% received drugs. Especially, eosinophils comprising more than 20% of the circulating leukocytes were mainly

Table 1. Incidence of causal diseases associated with eosinophilia

diseases	Number of Cases	% of Cases
Drugs		
penicillin analogues	76	15.2
carbamazepine	29	5.8
Allergic diseases		
asthma	36	7.2
allergic rhinitis	25	5.0
atopic dermatitis	9	1.8
urticaria	7	1.4
allergic vasculitis	1	0.2
Malignant diseases		
acute lymphoblastic leukemia	25	5.0
non-Hodgkin's diseases	8	1.6
brain tumor	7	1.4
Hodgkin's diseases	3	0.6
acute myeloblastic leukemia	2	0.4
sarcoma	15	3.0
Physiologic eosinophilia	17	3.4
Infectious diseases		
tuberculosis	5	1.0
streptococcal infection	3	0.6
pneumonia	2	0.4
febrile illness convalescent	2	0.4
Hematologic diseases		
anemia	7	1.4
myelofibrosis	1	0.2
Collagen disease		
rheumatoid arthritis	5	1.0
scleroderma	2	0.4
Parasite		
paragonimiasis	1	0.2
cysticercosis	1	0.2
Immunodeficiency disease		
Job's syndrome	1	0.2
Idiopathic hypereosinophilia syndrome	1	0.2
Miscellaneous		
congenital heart diseases	22	4.4
chronic renal diseases	10	2.0
Kimura's diseases	2	0.4
splenectomy	1	0.2
hypoadrenocorticism	1	0.2
Unknown causes	173	34.6
Total	500	100.0

Table 2. Clinical conditions in which eosinophilia was observed

Conditions	Number of Cases	% of Cases
hypertrophy of tonsil & adenoid	20	11.6
strabismus	13	7.5
inguinal hernia	7	4.0
cleft palate	5	2.9
MCLS*	5	2.9
hemangioma	4	2.3
ITP**	4	2.3
ptosis	4	2.3
cryptorchidism	4	2.3
arthralgia	4	2.3
aseptic meningitis	3	1.7
hypospadia	3	1.7
hepatitis	3	1.7
others	94	54.3
Total	173	99.8

*MCLS: mucocutaneous lymph node syndrome
**ITP: idiopathic thrombocytopenic purpura

Table 3. Percentage distribution of diseases associated with various degrees of eosinophilia

Diseases	% of Eosinophils 6-10	11-20	over 20
Drugs	36 %	28 %	13 %
Allergic diseases	21	28	38
Malignant diseases	16	24	19
Physiologic eosinophilia	6	4	
Infectious diseases	4	2	6
Hematologic diseases	3	2	
Collagen diseases	2	2	
Parasites		1	6
Miscellaneous	12	7	19
Total	100	98	101

observed in patients with allergic diseases, malignant diseases or drug reactions.

DISCUSSION

Eosinophils normally comprise about 1-3% of the circulating leukocytes. The number of circulating eosinophils in children are somewhat higher than those in adults. Based on the experiences of several investigators, a consensus would set values per cubic millimeter at the normal mean of 125 for adults and 225 for children under 12 years of age. Boys give higher values than girls, and peak values are observed in the age range of 4 to 8 years. There is a marked diurnal variation in the level of circulating eosinophils with the highest level occurring late at night and the lowest in the morning. (Williams 1983)

Eosinophilia was observed in a number of clinical conditions. Williams (1983) has listed the causes of eosinophilia as parasitic infestations, allergic disorders, dermatitis, hypereosinophilic syndrome, gastrointestinal disorders, tumors, hereditary and miscellaneous causes. Bolt (1987) classified eosinophilia is associated with myeloproliferative disorders, hypereosinophilic syndrome or familial eosinophilia. Secondary or reactive eosinophila is noted in allergic disorders, parasitic disorders, skin diseases, autoimmune disorders, pulmonary diseases, infectious diseases, neoplasms or miscellaneous conditions.

In this study we found the causes of or conditions associated with eosinophilia to be as follows:

(1) Drugs, including penicillin and carbamazepine

(2) Allergic diseases, including bronchial asthma, urticaria, allergic rhinitis, atopic dermatitis and allergic vasculitis

(3) Malignant diseases, including acute lymphoblastic leukemia, non-Hodgkin's lymphoma, brain tumor, Hodgkin's disease, acute myeloblastic leukemia and sarcoma

(4) Physiologic eosinophilia

(5) Infectious diseases, including tuberculosis, streptococcal infection, pneumonia and febrile illness convalescence

(6) Hematologic diseases, including anemia and myelofibrosis

(7) Autoimmune diseases, including rheumatoid arthritis and scleroderma

(8) Parasitic infestations, including paragonimiasis and cysticercosis

(9) Immunodeficiency diseases, such as Job's syndrome

(10) Idiopathic hypereosinophilic syndrome

(11) Miscellaneous conditions such as congenital heart diseases, peritoneal dialysis or chro-

nic renal diseases, splenectomy, hypoadrenocorticism and Kimura's disease

(12) Eosinophilia of unknown cause

Eosinophilia of unknown cause included diseases or conditions other than those listed by Lukens (1972), Wintrobe (1981), Williams (1983), Weller (1984) and Boldt (1987), and those eosinophilia in this study were observed in the hypertrophy of tonsils and adenoids, strabismus, inguinal hernia, cleft palate, MCLS, hemangioma, ITP, ptosis, cryptorchidism and arthralgia. Drugs most commonly associated with eosinophilia include carbamazepine, gold, iodides, nitrofurantoin, para-aminosalicylic acid, penicillin analogues, phenytoin, streptomycin and sulfonamide. Marked eosinophilia was observed in a patient with iodide sensitivity. Administration of digoxin is also followed by eosinophilia. In this study drugs that caused eosinophilia were penicillin analogues and carbamazepine.

In allergic deseases eosinophilia is usually moderate, but in some instances, such as bronchial asthma or angioneurotic edema, it may be much higher. In the case of urticaria, eosinophilia may accompany acute but not chronic urticaria. In this study eosinophilia was mainly encountered with asthma and allergic rhinitis.

In skin diseases, dermatitis herpetiformis and pemphigus show the highest and most constant eosinophilia. The degree of eosinophilia often appeared to vary with the extent of involvement.

Eosinophilia is observed in neoplastic diseases of various types. It was thought to be associated with the dissemination of tumors or tumor necrosis and did not depend on the type of tumor involved. Occult tumors, particularly those undergoing necrosis, should be considered in cases of unexplained eosinophilia (Isaacson & Rapoport, 1946; Murray 1953). In this study eosinophilia was observed in patients showing good response to treatment but not at the time of the diagnosis of the disease.

Physiologic eosinophilia occurs during the first three months of life, when eosinophil counts may be three times higher than in adults (Williams, 1983). there are conflicting reports on the presence of eosinophilia in infectious diseases. Most acute bacterial or viral infections show eosinopenia. However, the association of eosinophilia with many infectious diseases has been reported, such as cat scratch disease, infectious lymphocytosis, chlamydial pneumonia in infancy, infectious mononucleosis and erythema infectiosum. Eosinophilia accompanies scarlet fever in the early stage, especially when constitutional symptoms are mild and the rash is slight or in the convalescent phase (Friedman *et al.*, 1935). Eosinophilia occurs in leprosy, after pneumococcal pneumonia, during some stages of tuberculosis and in acute rheumatic fever complicated with erythema multiforme. In contrast to the presence of eosinophilia in convalescence from chronic bacterial infection, the reduction in circulating eosinophil levels is the characteristic feature of acute bacterial infection. Of fungal diseases, eosinophilia is associated with only three: bronchopulmonary aspergillosis, coccidioidomycosis and oromucocutaneous candidiasis.

In hematologic diseases, eosinophilia is common in myeloproliferative disorders, such as polycythemia vera, myelofibrosis, myeloid metaplasia, chronic myelogenous leukemia and is also observed in pernicious anemia, sickle cell anemia and leukemoid reactions (Wintrobe 1981). In this study iron deficiency anemia showed eosinophilia.

Eosinophilia has been observed in patients with connective tissue diseases such as rheumatoid arthritis, polyarteritis nodosa, Churg-Strauss syndrome, Henoch-Schönlein purpura, scleroderma or systemic lupus erythematosus. Patients with rheumatoid arthritis and eosinophilia had severe, deforming articular diseases and a high prevalence of rheumatoid vasculitis, pleuritis and subcutaneous nodules (Panushet *et al.*, 1971; Fischer, 1988). The magnitude of eosinophilia in parasitic infestations is dependent on the extent of the tissue invasion and the diagnostic stage. Parasitism in which tissue invasion is prominent is more regularly associated with eosinophilia than is intestinal parasitism. Parasites, such as Trichinella spiralis, that invade tissues cause the most pronounced eosinophilia. In the early stage of cysticercosis, moderate eosinophilia occurs, but this disappears when encystment takes place. In some helminths, such as hookworm and ascaris, eosinophilia is observed when larvae are traversing the lung before localization in the intestine.

Most of the instances of immunodeficiency associated with eosinophilia occurred in patients with abnormal T-cell function, such as Wiskott-

Aldrich syndrome, Job's syndrome, Nezelof syndrome or severe combined immunodeficiency disease. Eosinophilia is a prominent feature of graft versus host disease.

Eosinophilia has been observed in radiologic workers and in patients undergoing abdominal irradiation (Ghossein *et al.*, 1975). Eosinophilia has also been described in congenital syndromes such as cardiovascular defects, thrombocytopenia with absent radius and short-limbed dwarfism, but there is too little known about its pathogenesis to speculate on the eosinophilogenic mechanism in these situations (Mehrizi & Rowe 1966). In this study eosinophilia was found in children with congenital syndromes such as inguinal hernia, esotropia or exotropia, hypertrophy of the tonsils and adenoids, cleft palate or congenital heart disease.

In this study eosinophilia was mainly observed in patients with drug reactions, allergic diseases, malignant diseases or infectious diseases. In contrast, the studies carried out 20 years ago (Cho *et al.*, 1973; Koh *et al.*, 1975) revealed that parasitic infestation was the most common cause of eosinophilia in Korean children. Boldt (1987) reported that the most common cause for mild eosinophilia in hospitalized patients was drug allergy.

In the study of Stickney and Heck (1944), eosinophils comprising more than 20% of the circulating leukocytes were observed in allergic diseases, blood dyscrasias and lymphoblastoma, nonparasitic infection or dermatoses. In this study eosinophils comprising more than 20% of the circulating leukocytes were mainly observed in patients with allergic diseases, malignant diseases or drug reactions.

Using all these results, it can be concluded that eosinophilia in childhood is mainly associated with allergic diseases, malignant diseases or drug reactions, and of these three causes drug reaction is the most frequent one.

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= 국문초록 =

소아에서 호산구증다증을 동반하는 질환

서울대학교 의과대학 소아과학교실

김중곤 · 안효섭

1988년 9월부터 1989년 2월까지 서울대학교 소아병원을 방문한 소아중 호산구증다증을 나타내는 환아 500명을 대상으로 호산구증다의 원인 또는 동반되는 질환에 대해 조사하였다.

호산구의 증다는 약물 반응 (105례), 알레르기 질환 (76례), 악성 종양 (60례) 환아에서 주로 나타났다. 약물반응은 페니실린제제 (76례)나 항경련제, 특히 carbamazepine (29례)의 사용시 나타났다. 알레르기 질환으로는 천식 (36례), 알레르기 비염 (25례), 아토피 피부염 (9례), 담마진 (7례), 알레르기 혈관염 (1례)이 나타났다. 악성종양으로는 급성 림프구성 백혈병 (25례), 임프종양 (10례), 급성 골수성 백혈병 (2례), 육종 (15례)이 호산구증다증을 동반하였다.

호산구가 혈액내 백혈구수의 20%이상은 알레르기 질환 (38%), 악성 종양 (19%), 약물 반응 (13%)에 의해서 나타났다.

소아에서의 호산구의 증다는 주로 알레르기 질환, 악성 종양, 약물 반응에 의해 나타나며 특히 약물 반응에 의한 것이 제일 빈도가 높게 나타났다.