Original Article

Hypereosinophilia in Children and Adults: A Retrospective Comparison

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What is already known about this topic? Aside from a handful of case reports and a small case series, little is known about the clinical presentation, ultimate diagnosis, treatment, and prognosis of hypereosinophilia and hypereosinophilic syndrome in children.

What does this article add to our knowledge? This article characterizes and compares the clinical presentation, treatment, and prognosis of hypereosinophilia and hypereosinophilic syndrome in children and adults.

How does this study impact current management guidelines? In view of the remarkable similarities between hypereosinophilic syndrome in children and adults, recommended diagnostic and treatment algorithms for adults with eosinophilia are likely to be applicable to the pediatric population.

BACKGROUND: The differential diagnosis of hypereosinophilia is broad and includes asthma, atopic disease, drug hypersensitivity, parasitic infection, connective tissue disorders, malignancy, and rare hypereosinophilic disorders. Hypereosinophilia in children has not been well characterized to date.

OBJECTIVE: The objective of this study was to identify the common causes of marked eosinophilia in children and to characterize and compare the clinical symptoms at presentation, laboratory findings, final diagnosis, and therapeutic responses between children and adults with hypereosinophilic syndromes.

METHODS: A retrospective analysis of consecutive subjects evaluated for unexplained eosinophilia ≥ 1.5 × 10^9/L was conducted. All subjects underwent standardized clinical and laboratory evaluations with yearly follow-up. Clinical and laboratory parameters, final diagnoses, treatment responses, and outcomes were assessed. Medians and proportions were compared using Mann-Whitney *U* and Fisher Exact tests, respectively.

RESULTS: Of the 291 subjects evaluated, 37 (13%) were children and 254 were adults (87%). Whereas the frequencies of clinical hypereosinophilic syndrome (HES) variants were similar between children and adults, primary immunodeficiency was a more common secondary cause of HES in children (5% vs 0.4% in adults). Excluding subjects with treatable secondary causes, the median peak absolute eosinophil count was increased in pediatric subjects (9376 vs 5543/μL; $P = .002$), and children had more gastrointestinal complaints (62% vs 34%; $P = .003$) and less pulmonary involvement (34% vs 59%; $P = .01$) than adults. Despite these differences, corticosteroid responsiveness and overall prognosis were similar between the 2 groups.

CONCLUSIONS: Although children with HES often present with higher peak eosinophil counts than adults, the differential diagnosis, clinical characteristics, and prognosis of HES are similar in the 2 groups. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology
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Hypereosinophilic syndromes (HES) are a heterogeneous group of disorders defined by hypereosinophilia (HE; peripheral blood eosinophilia ≥ 1.5 ×10^9/L on at least 2 occasions or evidence of prominent tissue eosinophilia associated with symptoms and marked peripheral blood eosinophilia) and evidence of end organ damage attributable to the eosinophilia.[1-3] Although HES is most common in adults aged 20-50 years, it

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Abbreviations used

AEC- Absolute eosinophil count
ALL- Acute lymphoblastic leukemia
EAE- Episodic angioedema and eosinophilia
EGID- Eosinophilic gastrointestinal disease
EGPA- eosinophilic granulomatosis with polyangiitis
FE- familial eosinophilia
FP- FIP1L1/PDGFRA
FIP1L1-PDGFRA- Fip1-like 1-platelet-derived growth factor receptor alpha
HE- hypereosinophilia
HES- hypereosinophilic syndrome
HE_{US}- hypereosinophilia of unknown significance
IHES- idiopathic hypereosinophilic syndrome
LHES- lymphocytic variant HES
MHES- myeloproliferative variant HES
NIH- National Institutes of Health
TRG- T-cell receptor-γ gene

has been reported in children as young as 1 year old.[4] Aside from single case reports and small case series, little is known about the clinical presentation, ultimate diagnosis, treatment, and prognosis of HE and HES in children.[4-9]

Evaluation and treatment of pediatric patients with HE is challenging. As in adults, the underlying cause is often difficult to determine; the differential diagnosis includes asthma, atopic disease, drug hypersensitivity, parasitic infection, connective tissue disorders, malignancy, and rare hypereosinophilic syndromes. Because secondary causes, such as helminth infection and drug hypersensitivity, can cause a clinical picture indistinguishable from other forms of HES, it is important to identify disorders for which treatment is directed at the underlying cause rather than the eosinophilia itself. Equally important from a therapeutic and prognostic standpoint is the distinctions between hypereosinophilia of unknown significance (HE_{US}), myeloproliferative, lymphocytic variant, and idiopathic HES (IHES).[10-12]

The paucity of data on pediatric HES is likely multifactorial, but due in large part to the heterogeneity of clinical manifestations and the incorrect perception that HES is a disease of adults. To begin to address these issues, we conducted a retrospective analysis of all subjects referred to our institution for evaluation of unexplained HE over an 18-year period. Demographic; clinical and laboratory data, including diagnosis, signs, and symptoms at initial presentation; laboratory findings; and therapeutic response were compared between children and adults.

PATIENT POPULATION AND METHODS

All subjects evaluated at the National Institutes of Health (NIH) between February 1, 1994, and December 31, 2012, on a research protocol to study unexplained eosinophilia (NCT00001406) and who were found to have a peripheral absolute eosinophil count (AEC) of $\geq 1.5 \times 10^9$/L on at least 2 occasions at least 1 month apart were included in this retrospective analysis. Subjects aged 0-18 years at the time of the initial NIH evaluation were grouped as pediatric. Demographic, clinical and laboratory data pertaining to baseline characteristics, and treatment responses were collected by a retrospective chart review. Data were entered into a database without personal identifiers and compiled for analysis. All subjects signed informed consent on a National Institute of Allergy and Infectious Diseases-Institutional Review Board approved protocol.

A total of 297 subjects underwent detailed evaluation, including a complete history, physical examination, and laboratory testing, at baseline and at least yearly thereafter. The presence of the *FIP1L1/PDGFRA* (Fip1-like 1-platelet-derived growth factor receptor alpha—FP) mutation was determined by nested PCR or fluorescence *in situ* hybridization. T-cell clonality was assessed by T-cell receptor-γ (TRG) gene rearrangement studies, and aberrant T lymphocyte populations, most commonly CD3-$CD4^+$, by whole blood flow cytometry as previously described.[12,13] Parameters previously shown[14,15] or suspected to have prognostic significance in HES, including peak eosinophil count, serum tryptase, serum IgE, and vitamin B12 level, FP mutation status, T-cell phenotype, and clonality were assessed at the baseline visit and then yearly at follow-up visits. Subjects also underwent computed tomography of the chest, abdomen, and pelvis, electrocardiogram, echocardiogram, and pulmonary function tests to evaluate for end organ involvement. When available, bone marrow pathology was reviewed. Normal values were defined as follows: IgE < 100 IU/mL, tryptase < 11.5 ng/mL, and vitamin B12 < 950 pg/mL.

Final diagnoses were determined and subjects classified based on diagnostic criteria and clinical history. HE was defined as peripheral blood eosinophilia $\geq 1.5 \times 10^9$/L on at least 2 occasions or evidence of prominent tissue eosinophilia associated with symptoms and marked peripheral blood eosinophilia. HES was defined as HE with evidence of end organ damage attributable to eosinophilia.[3]

Several clinical subtypes of HES have been described.[2,16] Subjects with associated HES (HES in the setting of a secondary cause and for which treatment is directed at the underlying cause with no direct effect on the eosinophilia) or with transient HE/HES (HE/HES that resolved within 6 months in the absence of treatment) were identified and excluded from the analysis of clinical and laboratory features of HES. The remaining subjects were classified as follows: subjects with lymphocytic variant HES (LHES) were defined by the presence of an aberrant and/or clonal lymphocyte population in the peripheral blood.[17] Myeloproliferative HES (MHES) was used to designate subjects with myeloproliferative neoplasms and a known mutation, including subjects with FP, as well as subjects with HES and myeloproliferative features without a known mutation.[11] Overlap HES was the term used to describe subjects with eosinophilic involvement restricted to a single organ (ie, eosinophilic gastrointestinal disease) and peripheral eosinophilia $\geq 1.5 \times 10^9$/L and subjects with clinical features of eosinophilic granulomatosis with polyangiitis (EGPA), including asthma and sinusitis, peripheral eosinophilia $\geq 1.5 \times 10^9$/L, and no pathologic evidence of eosinophilic vasculitis on tissue biopsy. Subjects with familial eosinophilia were diagnosed on the basis of autosomal dominant transmission of peripheral hypereosinophilia over a minimum of 3 generations.[18] HE_{US} was defined by marked eosinophilia (AEC $\geq 1.5 \times 10^9$/L) in the absence of clinical manifestations of disease for a minimum of 5 years without treatment.[12] This was included in the spectrum of HES rather than HE, because patients who present with HE_{US} may develop clinical manifestations over time.[19] Episodic angioedema and eosinophilia (EAE) was defined by recurrent attacks of angioedema and eosinophilia occurring at approximately monthly intervals in the absence of therapy.[20,21] The remaining subjects were classified as IHES.

Disease duration was defined in months from onset of HE through date of resolution of eosinophilia and clinical manifestations, off-study protocol date, death, or December 31, 2012. Follow-up duration was defined in months from the subject's date of first visit at the NIH through the last follow-up contact (eg, off-study