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Hypereosinophilia in children and adults: a retrospective comparison

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Abstract

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—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 $1.5 \times 10^9/L$ 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 subjects (13%) were children and 254 were adults (87%). Whereas the frequencies of clinical 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 ; $p=0.002$), and children had more gastrointestinal complaints (62% vs. 34%; $p=0.003$) and less pulmonary involvement

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(34% vs. 59%; $p=0.01$) than adults. Despite these differences, corticosteroid responsiveness and overall prognosis were similar between the two groups.

Conclusions—Although children with hypereosinophilic syndrome (HES) often present with higher peak eosinophil counts than adults, the differential diagnosis, clinical characteristics and prognosis of HES are similar in the two groups.

Keywords

Eosinophil; hypereosinophilic syndrome; pediatric; children

Introduction

Hypereosinophilic syndromes (HES) are a heterogeneous group of disorders defined by hypereosinophilia (HE; peripheral blood eosinophilia $\geq 1.5 \times 10^9/L$ on at least two 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 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. Since 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 (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. In order 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 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 two 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 retrospective chart review. Data were entered into a database without personal identifiers and compiled for analysis. All subjects signed informed consent on a NIAID-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. Presence of the *FIPIL1/PDGFR* (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 $1.5 \times 10^9/L$ on at least two 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 *FIPIL1/PDGFR*, 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 (i.e. eosinophilic gastrointestinal disease) and peripheral eosinophilia $1.5 \times 10^9/L$ and subjects with clinical features of Eosinophilic Granulomatosis with Polyangiitis (EGPA), including asthma and sinusitis, peripheral eosinophilia $1.5 \times 10^9/L$, and no pathologic evidence of eosinophilic vasculitis on tissue biopsy. Subjects with familial eosinophilia (FE) were diagnosed on the basis of autosomal dominant transmission of peripheral hypereosinophilia over a minimum of 3 generations (18). Hypereosinophilic of unknown significance (HE_{US}) was defined by marked eosinophilia (AEC $1.5 \times 10^9/L$) 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 idiopathic HES (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 (e.g. off-study protocol date, death, or December 31, 2012). Fisher's exact test was used to compare prevalence and the Mann–Whitney U-test for comparison of group means. A p-value of less than 0.05 was considered significant for all tests.

Results

Classification by clinical HES variant

A total of 291 subjects (37 children, 254 adults) with HE underwent detailed evaluation for unexplained HE at our institution from 1994 through 2012. A secondary treatable cause was identified in 14% of children and 10% of adults (p=NS; Table 1). The most common etiology of secondary hypereosinophilia in both children and adults was helminth infection, comprising 60% of the cases in children and 40% in adults (p=NS). Of note, all 3 cases in children were due to *Toxocara* species (visceral larva migrans); whereas the adults were diagnosed with strongyloidiasis (n=5), schistosomiasis (n=3, including one mixed infection with strongyloidiasis), onchocerciasis (n=1) and intestinal helminth infection (n=2). Other causes of secondary eosinophilia in our cohort included immunodeficiency (i.e. DOCK8 deficiency, X-linked lymphoproliferative disease), allergy (including drug hypersensitivity), neoplasms, sarcoidosis, and pemphigus. A primary immunodeficiency was diagnosed significantly more frequently in children (5% vs. <0.4% in adults, p<0.05). Neoplasm-associated eosinophilia was identified in 3% of the adults presenting with HE and in none of the children. Systemic disorders associated with immunodysregulation, such as sarcoidosis and pemphigus, were also absent in the pediatric cohort.

Among the remaining 261 subjects (32 children (12%) and 229 adults (88%)), IHES was the most common clinical subtype of HES in both children and adults (total 47%; 46% of children vs. 47% of adults; p=NS) (Table 1, Figure 2). Transient HE was seen in only one subject, an infant of a mother with HES who was eosinophilic at birth. The frequencies of LHES, myeloid disorders with eosinophilia and overlap disorders were similar in children and adults. Episodic angioedema and eosinophilia is an extremely rare disorder that has been reported in children, but was not seen in our small pediatric cohort. Similarly, although familial eosinophilia is an autosomal dominant disorder that presents at birth, the single subject referred for unexplained eosinophilia during the time frame of this study was an adult.

Baseline characteristics of the patient population

The median age at presentation for evaluation of HE was 10.5 years of age (range 0.25–18 years) in the pediatric population and 48 years of age in the adults (range 19–85 years). There was a significant male predominance in the pediatric cohort that was not present in the adults (72% vs. 50% males respectively; $p=0.02$). Race distribution was similar between the two groups.

Baseline clinical and laboratory characteristics for the subjects with HES, excluding those with treatable secondary causes, are summarized in Table 2. Although the median AEC at presentation was similar in children and adults (1376/ μ L vs. 1208/ μ L, respectively; $p=NS$), the median peak AEC at presentation was significantly increased in pediatric subjects (9376 vs. 5543/ μ L; $p=0.002$). Median serum vitamin B12 levels were also significantly increased in children (1034 pg/mL vs. 680 pg/mL in adults; $p<0.001$). Median hemoglobin in males was slightly lower in children than adults (13.6 g/dL vs. 14.1 g/dL; $p=0.03$), although anemia was equally frequent. Adults were more likely to have a clonal TRG rearrangement pattern (6% in children vs. 27% in adults; $p=0.01$), although the prevalence of phenotypically aberrant T cell populations was similar among children and adults. *FIPIL1-PDGFR*A status, platelet count, erythrocyte sedimentation rate, serum IgE level, number of subjects with serum IgE >416 IU/ mL, serum tryptase level, and number of subjects with elevated serum tryptase (>11.5 ng/dL) were comparable in the pediatric and adult cohorts.

Clinical manifestations and organ system involvement in pediatric and adult HES

As described in prior series, the clinical manifestations and organ system involvement in subjects with HES without a treatable secondary cause were varied, ranging from constitutional complaints and allergic symptoms to potentially fatal endomyocardial fibrosis and stroke (Supplemental table 1). Children had significantly more gastrointestinal complaints (62% vs. 34%; $p=0.003$); whereas pulmonary manifestations other than asthma, such as infiltrates and pleural effusions, were significantly increased in adults (59% vs. 34%; $p=0.01$). There was also a trend towards an increase in cardiac involvement, including valvular disease, pericarditis and endomyocardial fibrosis, in the adult cohort (16% vs. 3% in children; $p=0.06$). Constitutional complaints, such as fever and fatigue, and hematologic/oncologic manifestations including thrombus, splenomegaly, lymphadenopathy, and neoplasm, also tended to be increased in children (44% vs. 28% in adults; $p=0.07$; 50% vs. 34%; in adults $p=0.08$, respectively). The overall frequencies of dermatologic, neurologic, allergic, rheumatologic and hematologic manifestations were comparable in the pediatric and adult populations (Figure 1, Supplemental Table 1).

Treatment

The majority of subjects with HES received corticosteroids at some time during their management (total 79%; 72% of children, 80% of adults; Figure 3). Corticosteroid response, was defined as AEC <1.0 $\times 10^9$ and resolution of symptoms for > 1 week on a constant corticosteroid dose. Data was sufficient to evaluate corticosteroid responsiveness in 50% of the pediatric and 62% of the adult subjects with HES. Corticosteroid response was similar in children and adults with HES (88% vs. 83%; $p=NS$). Other medications commonly prescribed in study subjects with HES included hydroxyurea, interferon-alpha, imatinib, and

methotrexate (Figure 3). Anti-IL-5 antibody therapy (mepolizumab or reslizumab) was administered to 3 children and 32 adults with HES on clinical research protocols ($p=NS$). A total of 32 subjects (6 children and 26 adults) received no therapy. The most common reasons for this included the absence of clinical manifestations (i.e., a diagnosis of familial eosinophilia or HE_{US}) in 11 subjects, subject refusal of therapy based on assessment of disease severity/risk of complications and the perceived side effects of therapy in 8 subjects and resolution of symptoms and eosinophilia prior to institution of therapy in 5 subjects. All other treatments were prescribed in <10% of subjects (see Supplemental Table 2 for complete list).

Disease Outcomes

The median duration of disease for our subjects with HES was 64 months (65.5 months in children vs. 64 months in adults; $p=NS$) and the median length of evaluation at the NIH was 36 months (58.5 months in children vs. 35 months in adults; $p=0.14$). Among the 32 children with HES, there were no reported deaths and only one subject (3%) went on to develop a neoplasm during the study period (Table 3). Although 17/229 adults (8%) died and 7 (3%) eventually developed neoplasms, this was not statistically increased compared to the pediatric cohort. The frequency of resolution of symptoms and peripheral hypereosinophilia (AEC <500 μ L) off all HES-directed therapies was also comparable between children and adults (9% vs. 8%; $p=NS$). The remaining subjects (88% of children and 83% of adults) had ongoing HES at the time of analysis.

Discussion

Although the overall prevalence of HE is unknown, a recent study identified eosinophilia $>1.0 \times 10^9$ in 0.3% of 356,196 individuals who underwent a complete blood count with differential in a primary care setting (22). Given the known suppressive effect of fever, viral and bacterial infection on peripheral eosinophil count, this prevalence is likely an underestimate. Despite this, reports of pediatric HES are rare and limited to single case descriptions and small case series (4–9). Consequently, little is known about the causes, clinical presentation, treatment, and prognosis of HES in children. To our knowledge, this study represents the largest case series of pediatric patients with HE/HES seen at a single center to date and provides data on both initial presentation and long-term follow-up.

In a case report and review of the literature (4), Katz et al. report a male predominance in 38 children with HES. It should be noted that the prevalence of *FIP1L1-PDGFR*A in their cases is unknown since the overwhelming majority of cases they report were published prior to the availability of testing for this mutation. Nevertheless, male gender was also significantly more common in our pediatric HES cohort ($p=0.02$) but not among the adults, despite a comparable prevalence of *FIP1L1-PDGFR*A in the two groups. In contrast to our series, 36.8% of the patients in the prior report had HES associated with acute lymphoblastic leukemia (ALL) and an additional 18.4% had chromosomal abnormalities. This high prevalence of ALL likely reflects an overrepresentation of the most severe cases in the literature rather than the true prevalence in the community, and explains the high prevalence

of fever (20%), significant death rate (42%) and short mean survival (10.6 months) in their pediatric HES patients.

Marked variability in clinical presentation, prognosis, and therapeutic response has been described between clinical HES subtypes (10–12). Whereas the relative frequencies of these different subtypes are unknown even in the adult population, data from several large retrospective series suggests that LHES and MHES each account for 10–30% of patients with HES once patients with treatable secondary causes are excluded (10, 23–26). These data are confirmed in the present study and extended to the pediatric population. Associated HES was also similar in frequency between children and adults (10–15%). Secondary causes were varied and included parasitic infection, immunodeficiency, allergic disease or drug hypersensitivity, neoplasm, and disorders of immune dysregulation. Among these, only primary immunodeficiency was more common in children than adults (5% vs 0.4%, $p=0.04$), an unexpected finding since patients were not referred for evaluation of possible immunodeficiency.

Clinical manifestations were also similar between children and adults, with the exception of pulmonary involvement (excluding asthma), which was more frequent in adults, and gastrointestinal involvement, which was more frequent in children. Whereas most studies to date have suggested that eosinophilic gastrointestinal disease (EGID) is more prevalent in adults, a recent large study examining prevalence of EGID by subtype suggests that eosinophilic enteritis is more prevalent in children (27). Since eosinophilic enteritis is more likely to be associated with peripheral eosinophilia than eosinophilic esophagitis (the most common of the EGIDs), this could be one factor contributing to the increased prevalence of gastrointestinal involvement in our pediatric cohort. Although referral bias could also explain our findings, all subjects were referred to the NIH for evaluation of unexplained eosinophilia. Subjects referred for possible parasitic infection (or for whom the diagnosis was evident on referral) were enrolled on a separate screening protocol for suspected parasitic diseases. Subjects were referred from a variety of subspecialists, and referral patterns were similar for adults and children (data not shown).

One of the few striking differences between children and adults with HES was the median peak eosinophil count, which was almost twice as high in the pediatric patients despite comparable duration of follow-up. Despite this, mortality in pediatric patients was low and similar to that in the HES group as a whole. There were a total of 5 deaths during the study period; all in subjects with associated HES, two in subjects with immunodeficiency (one adult and one child) and 3 in adults with neoplasms. Types of therapeutic interventions were also similar between the two groups with corticosteroids by far the most common agent prescribed, followed by imatinib and hydroxyurea. Although the numbers of subjects treated precluded comparison of response rates for most of the agents prescribed, information on corticosteroid response was available for 16 children and 143 adults and was comparable. Therapeutic response rates to other treatments in children and adults should be evaluated in future studies.

This study was limited by the retrospective design and resultant variability in the depth of clinical data reported in and extracted from clinical progress notes. Despite these limitations,

our data suggest that the causes, clinical manifestations, treatment and prognosis of HE are similar in children and adults. Consequently, diagnostic and treatment algorithms developed for adults with HE are likely to be applicable to the pediatric population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CEP	Chronic eosinophilic pneumonia
DOCK8	Dedicator of cytokinesis 8 deficiency
EAE	episodic angioedema and eosinophilia
EFE	eosinophilic fasciitis with peripheral eosinophilia
EGE	eosinophilic GI disease with peripheral eosinophilia
EGPA	eosinophilic granulomatosis with polyangiitis
FE	familial eosinophilia
FIP1L1-PDGFRα	Fip1-like 1-platelet-derived growth factor receptor α
HES	hypereosinophilic syndrome
HEUS	hypereosinophilia of unknown significance
IHES	idiopathic hypereosinophilic syndrome
LHES	lymphocytic variant HES
MHES	myeloproliferative variant HES
MPN	myeloproliferative neoplasm
SPRED	Sprouty-related, EVH1 domain containing 1/2 immunodeficiency
XLP	X-linked lymphoproliferative disease

References

1. Chusid MJ, Dale DC, West BC, Wolff SM. The hypereosinophilic syndrome: analysis of fourteen cases with review of the literature. *Medicine*. 1975; 54(1):1–27. [PubMed: 1090795]
2. Klion AD, Bochner BS, Gleich GJ, Nutman TB, Rothenberg ME, Simon HU, et al. Approaches to the treatment of hypereosinophilic syndromes: a workshop summary report. *J Allergy Clin Immunol*. 2006; 117(6):1292–1302. [PubMed: 16750989]
3. Valent P, Klion AD, Horny HP, Roufosse F, Gotlib J, Weller PF, et al. Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes. *J Allergy Clin Immunol*. 2012; 130(3):607–612. e9. [PubMed: 22460074]
4. Katz HT, Haque SJ, Hsieh FH. Pediatric hypereosinophilic syndrome (HES) differs from adult HES. *J Pediatr*. 2005; 146(1):134–136. [PubMed: 15644839]
5. Chilcote RR, Pergament E, Kretschmer R, Mikuta JC. The hypereosinophilic syndrome and lymphoblastic leukemia with extra C-group chromosome and q14+ marker. *J Pediatr*. 1982; 101(1):57–60. [PubMed: 6953225]
6. Egesten A, Hagerstrand I, Kristoffersson U, Garwicz S. Hypereosinophilic syndrome in a child mosaic for a congenital triplication of the short arm of chromosome 8. *Br J Haematol*. 1997; 96(2):369–373. [PubMed: 9029027]
7. Farruggia P, Giugliano E, Russo D, Trizzino A, Lorenzatti R, Santoro A, et al. *FIPIL1-PDGFR* alpha-positive hypereosinophilic syndrome in childhood: a case report and review of literature. *J Pediatr Hem Onc*. 2014; 36(1):e28–e30.
8. Guitard AM, Horschowski N, Mozziconacci MJ, Michel G, George F, Capodano AM, et al. Hypereosinophilic syndrome in childhood: trisomy 8 and transformation to mixed acute leukaemia. *Nouv Rev Fr Hematol*. 1994; 35(6):555–559. [PubMed: 8152903]
9. Tono-oka T, Sato Y, Matsumoto T, Ueno N, Ohkawa M, Shikano T, et al. Hypereosinophilic syndrome in acute lymphoblastic leukemia with a chromosome translocation [t(5q;14q)]. *Med Ped Oncol*. 1984; 12(1):33–37.
10. Klion AD. How I treat hypereosinophilic syndromes. *Blood*. 2015; 126(9):1069–1077. [PubMed: 25964669]
11. Khoury P, Desmond R, Pabon A, Holland-Thomas N, Ware JM, Arthur DC, et al. Clinical features predict responsiveness to imatinib in platelet derived growth factor receptor alpha-negative hypereosinophilic syndrome. *Allergy*. 2016
12. Chen YY, Khoury P, Ware JM, Holland-Thomas NC, Stoddard JL, Gurprasad S, et al. Marked and persistent eosinophilia in the absence of clinical manifestations. *The J Allergy Clin Immunol*. 2014; 133(4):1195–1202. [PubMed: 23987798]
13. Roufosse F, de Lavareille A, Schandene L, Cogan E, Georgelas A, Wagner L, et al. Mepolizumab as a corticosteroid-sparing agent in lymphocytic variant hypereosinophilic syndrome. *J Allergy Clin Immunol*. 2010; 126:828–835. [PubMed: 20810155]
14. Klion AD, Noel P, Akin C, Law MA, Gilliland DG, Cools J, et al. Elevated serum tryptase levels identify a subset of patients with a myeloproliferative variant of idiopathic hypereosinophilic syndrome associated with tissue fibrosis, poor prognosis and imatinib responsiveness. *Blood*. 2003; 101:4660–4666. [PubMed: 12676775]
15. Lefebvre C, Bletry O, Degoulet P, Guillevin L, Bentata-Pessayre M, Du LTH, et al. Prognostic factors of hypereosinophilic syndrome. Study of 40 cases. *Ann Med Interne (Paris)*. 1989; 140(4):253–257. [PubMed: 2675714]
16. Simon HU, Rothenberg ME, Bochner BS, Weller PF, Wardlaw AJ, Wechsler ME, et al. Refining the definition of hypereosinophilic syndrome. *J Allergy Clin Immunol*. 2010; 126(1):45–49. [PubMed: 20639008]
17. Roufosse F, Cogan E, Goldman M. Lymphocytic variant hypereosinophilic syndromes. *Immunol Allergy Clin North Am*. 2007; 27(3):389–413. [PubMed: 17868856]
18. Rioux JD, Stone VA, Daly MJ, Cargill M, Green T, Nguyen H, et al. Familial eosinophilia maps to the cytokine gene cluster on human chromosomal region 5q31-q33. *Am J Hum Genet*. 1998; 63(4):1086–1094. [PubMed: 9758611]

19. Helbig G, Hus M, Francuz T, Dziaczowska-Suszek J, Soja A, Kyrzcz-Krzemien S. Characteristics and clinical outcome of patients with hypereosinophilia of undetermined significance. *Med Oncol*. 2014; 31(1):815. [PubMed: 24338273]
20. Gleich GJ, Schroeter AL, Marcoux JP, Sachs MI, O'Connell EJ, Kohler PF. Episodic angioedema associated with eosinophilia. *N Engl J Med*. 1984; 310(25):1621–1626. [PubMed: 6727934]
21. Khoury P, Herold J, Alpaugh A, Dinerman E, Holland-Thomas N, Stoddard J, et al. Episodic angioedema with eosinophilia (Gleich syndrome) is a multilineage cell cycling disorder. *Haematologica*. 2015; 100(3):300–307. [PubMed: 25527564]
22. Andersen CL, Siersma VD, Hasselbach HC, Lindegaard H, Vestergaard H, Felding P, et al. Eosinophilia in routine blood samples and the subsequent risk of hematological malignancies and death. *Am J Hematol*. 2013; 88(10):843–847. [PubMed: 23765950]
23. Ogbogu PU, Bochner BS, Butterfield JH, Gleich GJ, Huss-Marp J, Kahn JE, et al. Hypereosinophilic syndrome: a multicenter, retrospective analysis of clinical characteristics and response to therapy. *J Allergy Clin Immunol*. 2009; 124(6):1319–1325. e3. [PubMed: 19910029]
24. Simon HU, Plötz SG, Dummer R, Blaser K. Abnormal clones of T cells producing interleukin-5 in idiopathic eosinophilia. *N Engl J Med*. 1999; 341:1112–1120. [PubMed: 10511609]
25. Pardanani A, Brockman SR, Paternoster SF, Flynn HC, Ketterling RP, Lasho TL, et al. FIP1L1/PDGFRα fusion: prevalence and clinicopathologic correlates in 89 patients with moderate to severe eosinophilia. *Blood*. 2004; 104:3038–3045. [PubMed: 15284118]
26. Vaklavas C, Tefferi A, Butterfield RP, Ketterling RP, Vertovsek S, Kantarjian H, et al. Idiopathic" eosinophilia with an Occult T-cell clone: prevalence and clinical course. *Leuk Res*. 2007; 31:691–694. [PubMed: 17095087]
27. Jensen ET, Martin CF, Kappelman MD, Dellon ES. Prevalence of Eosinophilic Gastritis, Gastroenteritis, and Colitis: Estimates From a National Administrative Database. *J Pediatr Gastroenterol Nutr*. 2016; 62:36–42. [PubMed: 25988554]

Highlights Box

- 1.** 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.
- 2.** 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.
- 3.** 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.

Figure 1.

Clinical manifestations and organ involvement in subjects with HES. Bars represent the % of adults (black) or children (grey) with signs or symptoms consistent with involvement in each category. Patients with associated HES have been excluded from this analysis.

Gastrointestinal manifestations included abdominal pain, nausea/vomiting, diarrhea; dermatologic manifestations included rash, urticaria, angioedema; allergic manifestations included outside physician diagnostic history of asthma, allergic rhinitis, or sinusitis; hematologic manifestations included thrombus, splenomegaly, lymphadenopathy, neoplasm; constitutional manifestations included fever and fatigue; pulmonary manifestations included infiltrates identified with imaging and pleural effusion(s); rheumatologic manifestations included myalgia/arthritis and eosinophilic fasciitis; neurologic manifestations included clinical history of stroke or neuropathy; cardiac manifestations included valvular disease, endomyocardial fibrosis, pericarditis, elevated troponin. * $p < 0.05$, ** $p < 0.01$, Mann-Whitney test

Figure 2.

Frequency of clinical variants among patients presenting with HE/HES. Bars represent the % of adults (black) or children (grey) meeting the diagnostic criteria for each HE/HES variant. IHES refers to idiopathic hypereosinophilic syndrome; overlap disorder includes those subjects with evidence of single organ disease and peripheral eosinophilia $1.5 \times 10^9/L$ or evidence of a clinical overlap between Eosinophilic Granulomatosis with Polyangiitis and HES; myeloproliferative disorders with eosinophilia includes those subjects with myeloproliferative variant HES, those with myeloproliferative disease and a known mutation, and those with chronic eosinophilic leukemia-not otherwise specified; LHES refers to lymphocytic variant HES; and FE refers to familial eosinophilia.

Figure 3.

Prescribed treatments in patients with HES. Bars represent the % of adults (black) or children (grey) who received the specified therapy prior to or during the course of the study. Patients with associated HES have been excluded from this analysis. Corticosteroids included prednisone, prednisolone, and methylprednisolone.

Table 1

Clinical variants in children and adults presenting with HE/HES (n=291)

Diagnosis*	Children (n=37)	Adults (n=254)	P-value
Myeloproliferative HE/HES	3 (8%)	27 (11%)	NS
PDGFRA-associated MPN	2	17	NS
MPN with other known mutation**	0	9	NS
MHES with unknown mutation	1	1	NS
LHES***	2 (5%)	41 (16%)	NS
Non-cyclic LHES	2	36	NS
EAE	0	5	NS
Overlap HES	8 (22%)	31 (12%)	NS
EGPA	2	9	NS
EFE	1	3	NS
EGE	5	15	NS
CEP	0	4	NS
Associated HE/HES	5 (14%)	25 (10%)	NS
Parasitic helminth infection	3	10	NS
Neoplasm	0	7	NS
Immunodeficiency†	2	1	0.04
Allergic etiology	0	4	NS
Other	0	3	NS
IHES	17 (46%)	120 (47%)	NS
Transient IHES	1	0	NS
Sustained IHES	16	120	NS
HE _{US}	2 (5%)	9 (3%)	NS
Familial HE/HES	0 (0%)	1 (<1%)	NS

* Abbreviations: CEP: Chronic eosinophilic pneumonia; EAE: episodic angioedema and eosinophilia; EFE: eosinophilic fasciitis with peripheral eosinophilia; EGE: eosinophilic GI disease with peripheral eosinophilia; EGPA: eosinophilic granulomatosis with polyangiitis; HE: hypereosinophilia; HES: hypereosinophilic syndrome; HEUS: hypereosinophilic of unknown significance; IHES: idiopathic hypereosinophilic syndrome; LHES: lymphocytic variant HES; MHES: myeloproliferative variant HES; MPN: myeloproliferative neoplasm; PDGFRA: platelet-derived growth factor receptor alpha.

** Includes those with MPN due to Janus Kinase 2 (JAK2), D816VKIT, chronic myelomonocytic leukemia, and atypical chronic myeloid leukemia.

*** Subjects with clonal or aberrant T cell populations with a concomitant diagnosis of MPN (n=3), chronic lymphocytic leukemia (n=2), EGPA overlap (n=7), HEUS (n=5) or FE (n=1) are excluded.

† One case each of Dedicator of cytokinesis 8 (DOCK8) deficiency and sprouty-related, EVH1 domain containing 1/2 (SPRED) immunodeficiency in the pediatric group and one case of X-linked lymphoproliferative disease (XLP) in the adult group.

Table 2

Clinical and laboratory characteristics at baseline for subjects with HES *

Characteristic	Children (n=32)	Adults (n=229)	P-value
Gender (M/F)	23/9	115/114	0.02
Race/Ethnicity			NS
White	18 (56%)	186 (81%)	
Black	5 (16%)	19 (8%)	
Asian	2 (6%)	12 (5%)	
Hispanic	7 (22%)	9 (4%)	
Other	0 (0%)	3 (1%)	
Median age at presentation in years (range)	10.5 (0.25–18)	48 (19–85)	<0.001
Median AEC/μL at presentation (range)	1376 (84–56180)	1208 (0–27555)	NS
Median peak AEC/μL (range)	9376 (1780–100000)	5543 (480–120000)	0.002
Median serum IgE in IU/mL (range)	183 (5–42874)	136 (1–23200)	NS
No. with serum IgE >416 IU/mL (%)	10/31 (32%)	67/222 (30%)	NS
Median serum vitamin B12 in pg/mL (range)	1034 (362–8396)	680 (172–27529)	<0.001
No. with serum vitamin B12 >1000 pg/mL (%)	12/26 (46%)	65/216 (30%)	NS
Median serum tryptase in ng/mL (range)	5.7 (1.2–19.9)	6.1 (0–700)	NS
No. with serum tryptase >11.5 ng/mL (%)	6/28 (21%)	40/207 (19%)	NS
Median Hgb in g/dL (range)			
Male	13.6 (8.3–16)	14.1 (6.9–16.6)	0.03
Female	12.4 (5.8–14.2)	12.8 (8.8–15.6)	NS
No. with anemia ** (%)	4/32 (13%)	54/222 (24%)	NS
Median platelets in K/μL (range)	278 (73–720)	272 (42–571)	NS
Median ESR in mm/hr (range)	8 (2–111)	12 (1–119)	NS
No. with elevated ESR (%)	8/29 (28%)	67/222 (30%)	NS
<i>FIPIL1</i> - <i>PDGFRA</i> +	1/30 (3%)	16/216 (7%)	NS
Clonal TCR rearrangement	2/31 (6%)	58/214 (27%)	0.01

Characteristic	Children (n=32)	Adults (n=229)	P-value
Aberrant T cell phenotype ***	1/31 (3%)	22/214 (10%)	NS

* Patients with associated HES have been excluded from this analysis.

** defined using the normal values for age and gender of the Department of Laboratory Medicine, Clinical Center, NIH.

*** CD3-CD4+ T cells in all but two adult subjects who had aberrant populations of CD3+CD4+CD8+ T cells.

Table 3Clinical outcomes in subjects with HES^{*}

Outcome	Children (n=32)	Adults (n=229)	P-value
Median disease duration in months (range)	65.5 (9–191)	64 (0–596)	NS
Median duration of follow-up in months (range)	58.5 (2–187)	35 (0–267)	NS
Outcome			
Persistent HES ^{**}	28 (88%)	191 (83%)	NS
Resolution of HES ^{***}	3 (9%)	17 (8%)	NS
Death	0 (0%)	17 (8%)	NS
Development of neoplasm	1 (3%)	7 (3%)	NS

^{*} Patients with associated HES have been excluded from this analysis.

^{**} defined as clinical evidence of disease at the time the patient went off-protocol, was lost to follow-up, or study end date.

^{***} defined as resolution of peripheral hypereosinophilia (AEC < 500/μL) and active clinical manifestations of HES off all HES-directed therapy.