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Evidence of helminthic infestation and efficacy of anthelminthic treatment in children investigated for eosinophilia

Dokazi infestacije helmintima i učinak terapije antihelminticima kod dece ispitivane zbog eozinofilije

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Abstract

Background/Aim. The cause of eosinophilia often remains unelucidated. The aim of the study was to analyze causes and treatment approaches in children with eosinophilia in pediatric tertiary care hospital. **Methods.** The medical records of children investigated for eosinophilia (based on the International Classification of Diseases code D72.1) were retrospectively reviewed in the University Children's Hospital, Belgrade, Serbia, from December 2011 to December 2022. A total of 105 children (62 boys; male:female ratio was 1:4) aged one month to 16.5 years (median 7.7 years) were diagnosed with eosinophilia. After excluding 15 of them due to incorrectly assigned diagnosis based on relative eosinophil number only, the remaining 90 children were grouped according to the severity of eosinophilia (mild, moderate or severe). **Results.** Serological analysis confirmed toxocariasis in six (6.7%) patients, while two (2.2%) had a confirmed nematode infestation (*Ascaris lumbricoides* and *Enterobius vermicularis*, respectively). Thirty-two (35.6%) children with eosinophilia and three with no true eosinophilia were diagnosed with helminthiasis *ex juvantibus*. Eosinophilia was ultimately explained by allergic/atopic conditions [19 (21.1%)], drug reactions [four (4.4%)], bacterial infections [nine (8.9%)], hematological problems [five (5.5%)], autoimmune disorders [three (3.3%)], unrelated congenital disorders (one), or as an isolated finding [seven (7.8%)]. In addition, one of the children without an increased absolute eosinophil number was diagnosed with eosinophilic esophagitis. A total of 56 (53.3%) children received anthelminthic treatment: 9 (90.0%) with severe eosinophilia, 19 (51.4%) with moderate, 23 (53.5%) with mild, and 5 (33.3%) children with no true eosinophilia. Most (42) of the children were given mebendazole only, while the remaining 14 (eight with severe, three with moderate, and three with mild) were also initially treated with mebendazole but subsequently shifted to albendazole due to the persistence of eosinophilia. In all treated children, eosinophilia and other relevant findings (if any) subsided in a matter of a few days to a few weeks after initializing treatment. **Conclusion.** Our results support the recommendation that unexplained eosinophilia of all levels of severity requires a standardized diagnostic approach. The results also provide some support for a potential rational basis for *ex juvantibus* administration of anthelminthic drugs in a fraction of children with eosinophilia without an obvious etiological explanation.

Key words:
anthelmintics; child; diagnosis; diagnosis, differential; eosinophilia; tertiary care centers; treatment outcome.

Apstrakt

Uvod/Cilj. Uzrok eozinofilije često ostaje nerasvetljen. Cilj rada bio je da se analiziraju uzrok i terapijski pristup kod dece sa eozinofilijom u pedijatrijskoj bolnici tercijarnog stepena zbrinjavanja. **Metode.** Retrospektivno je analizirana medicinska dokumentacija dece koja su ispitivana zbog eozinofilije (naznačene šifrom D72.1 na osnovu Međunarodne klasifikacije bolesti) u Univerzitetskoj dečjoj klinici u Beogradu, Srbija, u periodu od decembra 2011. do decembra 2022. Dijagnozu eozinofilije imalo je ukupno 105 dece (62 dečaka; odnos dečaci:devojčice iznosio je 1:4) uzrasta od mesec dana do 16,5 godina (medijana 7,7 godina). Posle isključenja 15 dece zbog pogrešno postavljene dijagnoze samo na osnovu relativnog broja eozinofila, preostalih 90 dece grupisano je prema težini eozinofilije (blaga, umerena ili teška). **Rezultati.** Serološkom analizom potvrđena je toksokarijaza kod šest (6,7%) bolesnika, dok je kod dvoje dece (2,2%) dokazana infestacija nematodama (*Ascaris lumbricoides*, odnosno *Enterobius vermicularis*). Kod 32 (35,6%) dece sa eozinofilijom, kao i kod troje dece bez prave eozinofilije, helmintijaza je dijagnostikovana *ex juvantibus*. Eozinofilija je na kraju objašnjena

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alergijskim/atopijskim stanjima [19 (21,1%)], reakcijama na lekove [četiri (4,4%)], bakterijskim infekcijama [devet (8,9%)], hematološkim problemima [pet (5,5%)], autoimunskim bolestima [tri (3,3%)], nepovezanim urođenim stanjima (jedno dete) ili kao izolovan nalaz [sedam (7,8%)]. Pored toga, kod jednog deteta s dijagnozom eozinofilije ali ne i povišenim apsolutnim brojem eozinofila postavljena je dijagnoza eozinofilnog ezofagitisa. Ukupno 56 (53,3%) dece dobilo je terapiju antihelminticima: 9 (90,9%) sa teškom eozinofilijom, 19 (51,4%) sa umerenom, 23 (53,5%) sa blagom i 5 (33,3%) dece bez prave eozinofilije. Većina (42) dece dobila je samo mebendazol, dok je preostalih 14 (osmoro sa teškom, troje sa umerenom i troje sa blagom) takođe prvobitno lečeno mebendazolom, ali su kasnije, zbog perzistentnosti eozinofilije, lečeni albendazolom. Kod sve dece lečene antihelminticima, eozinofilija i ostali relevantni nalazi (ako ih je bilo) povukli su se u roku od nekoliko dana do nekoliko nedelja od početka lečenja. **Zaključak.** Naši rezultati u celini govore u prilog preporuke da neobjašnjena eozinofilija bilo kog stepena težine iziskuje standardizovani dijagnostički pristup. Takođe, rezultati potkrepljuju potencijalnu racionalnu osnovu za primenu antihelmintika *ex juvantibus* kod jednog broja dece sa eozinofilijom bez očiglednog etiološkog razjašnjenja.

Ključne reči:
antihelmintici; deca; dijagnoza; dijagnoza, diferencijalna; eozinofilija; zdravstvene ustanove, tercijarne; lečenje, ishod.

Introduction

Eosinophilia is defined as an absolute blood eosinophil count above 0.5×10^9/L [1]. As a rather nonspecific finding, eosinophilia can accompany a wide range of allergic, autoimmune, and infectious disorders, notably those caused by eukaryotic organisms – protozoa and multicellular parasites (helminths) [2]. Eosinophilia is also the hallmark of rare but highly significant primary eosinophilic syndromes [3]. This breadth of potential clinical implications of eosinophilia is in line with the wide array of roles played by eosinophil granulocytes – an evolutionarily ancient part of our immune system – in health and disease [4].

Even though eosinophilia is a common finding (and no less commonly incidental), its exact cause often remains unelucidated [5]. This is partly due to the transient and fluctuating nature of eosinophilia in many known disorders, as well as in the case of parasitic eosinophilia due to the limited sensitivity of routine parasitological tests [6]. However, at least a fraction of unexplained eosinophilia is likely to result from the absence of (or insufficient adherence to) standard guidelines or protocols for physicians investigating patients with eosinophilia, particularly in the pediatric population, where parasitic infestations are more prevalent relative to adults, and primary (genetically determined or influenced) causes of eosinophilia are more likely to present. Among helminthic infestations, toxocariasis appears to be particularly elusive, underdiagnosed, and prone to bring about potentially serious consequences [7–9].

The aim of the study was to present and analyze the diagnostic workup of patients with eosinophilia in a tertiary care pediatric institution, with particular emphasis on the evidence of potential helminthic infestation and the documentation of its specific treatment (including that administered *ex juvantibus*).

Methods

This retrospective study reviewed medical records of children investigated for eosinophilia in the University Children's Hospital, Belgrade, Republic of Serbia, from December 2011 to December 2022. This work has been approved by the Ethical Review Board of the University Children's Hospital (No. 16/9, from February 8, 2024).

All children who have been assigned the diagnosis of eosinophilia [based on the International Classification of Diseases (ICD) code D72.1] were included in the analysis. This criterion was met by a total of 105 children (62 boys and 43 girls, male:female ratio was 1:4) aged one month to 16.5 years (median 7.7 years). Fifteen (14.2%) children were excluded because they had been incorrectly assigned the diagnosis of eosinophilia based on the relative number of eosinophils, while the absolute number was below the cut-off value for this diagnosis (0.5×10^9/L). The patients were divided into subgroups according to the severity of their eosinophilia: mild [$0.5–1.5 \times 10^9$/L, n = 43 (47.8%)], moderate [$1.5–5.0 \times 10^9$/L, n = 37 (41.1%)], or severe [$> 5.0 \times 10^9$/L, n = 10 (11.1%)]. The patients were further grouped according to whether they were referred to our hospital from primary healthcare institutions due to eosinophilia *per se* or were diagnosed during diagnostic workups conducted for various clinical indications. These indications were then broadly grouped according to the organ system that was primarily affected.

All patients had an automatic complete blood count (CBC) with additional leukocyte differential count conducted non-automatically (using optical microscopy). The eosinophils were enumerated on a smear stained according to Leischman. In addition to CBC, data on relevant clinical parameters and laboratory findings, including parasitological investigations (stool examination for parasite ova, serological tests for toxocariasis), bone marrow examination (if performed), and other relevant findings were collected and analyzed. Information on anthelminthic treatment (AT) and its efficacy was also noted.

Results

Indications for investigation

In 44 (41.9%) children, CBC was performed upon referral from a primary healthcare institution due to

eosinophilia, while in 61 (58.1%) children, the indication for this investigation was set in the course of clinical examination in our hospital. The general types of these indications are presented in Table 1. The most prevalent indications were gastroenterological [22 (24.4%), e.g., abdominal pain], followed by hematological [18 (20.0%), e.g., leukocytosis, splenomegaly, enlarged lymph nodes], and immunological/allergological indications [9 (10.0%), e.g., asthma, urticaria].

Final diagnosis

We classified our patients (including those investigated based on relative eosinophile numbers only) into broad groups according to the final diagnosis (Table 2). Toxocariasis was serologically confirmed in six patients (6.7%), while two (2.2%) had a confirmed nematode infestation, *Ascaris* (*A.*) *lumbricoides* and *Enterobius vermicularis*, respectively. In addition, 32 (35.6%) children, or 35 (33.3%) of a combined series, including those with no true eosinophilia, were diagnosed with helminthiasis based on the success of tentative AT (*ex juvantibus*). Eosinophilia was explained by allergic/atopic conditions in 19 (21.1%) patients, while four (4.4%) had a drug reaction, three of whom satisfied some or all criteria for drug reaction with eosinophilia and systemic symptoms (DRESS). Eosinophilia was associated with bacterial infections in nine (8.9%) children: respiratory infections in four, streptococcal angina in two, and otitis media, urinary infection, and acute appendicitis in one child each. Five (5.5%) patients had a hematological problem (severe anemia in two, leukopenia in one, and isolated splenomegaly in one). Three children were found to suffer from autoimmune disorders (inflammatory bowel disease, diabetes mellitus type 1, and autoimmune uveitis, respectively). Two children with D72.1 designation (one of whom did not have eosinophilia) were diagnosed with congenital syndromes (not belonging to the group of hypereosinophilic syndromes): sodium voltage-gated channel alpha subunit 2A (SCN2A)-spectrum epileptic syndrome and familial adenomatous polyposis, respectively. One of the children excluded from the series was diagnosed with eosinophilic esophagitis. In seven (7.8%) children, eosinophilia turned out to be an isolated and transient finding, while three (3.3%) were never brought to us by their parents for a follow-up visit.

Table 1

Indications for eosinophilia investigation and severity of the observed eosinophilia

Parameter	Eosinophilia (severity)				Total eosinophilia	Total (D72.1)
	none	mild	moderate	severe		
Referred for eosinophilia	10	16	13	5	34	44
Indication set at UCH	5	27	24	5	56	61
Σ	15	43	37	10	90	105
Gastroenterologist	2	12	8	2	22	24
Hematologist	0	7	10	1	18	18
Immunologist/allergologist	2	5	3	1	9	11
Pulmonologist	0	1	1	1	3	3
Nephrologist	0	1	0	0	1	1
Infectologist	0	1	1	0	2	2
Other	1	0	1	0	1	2
Σ	5	27	24	5	56	61

UCH – University Children's Hospital. All values are given as numbers.

Table 2

Final diagnosis in patients with different degrees of eosinophilia

Parameter	Eosinophilia (severity)				Total eosinophilia	Total (D72.1)
	none	mild	moderate	severe		
Isolated eosinophilia	3	2	5	0	7	10
Helminthiasis *ex juvantibus*	3	15	12	5	32	35
Toxocariasis	0	1	2	3	6	6
Nematode infestation	0	0	1	1	2	2
Allergic/atopic disorders	5	9	10	0	19	24
Drug reaction/[1]DRESS	0	2	1	1	4	4
Bacterial infections	1	4	4	0	8	9
Hematological disorders	0	3	2	0	5	5
Autoimmune disorders	0	3	0	0	3	3
Congenital syndromes	1	1	0	0	1	2
Eosinophilic esophagitis	1	0	0	0	0	1
Lost to follow-up	1	3	0	0	3	4
Σ	15	43	37	10	90	105

[1] Three patients out of the total number of drug reactions fulfilled the criteria for drug reaction with eosinophilia and systemic symptoms (DRESS).
All values are given as numbers.

Parasite detection

Stool examination for parasite ova was performed in 34 (32.4%) patients: 10 (100.0%) patients with severe eosinophilia, 17 (45.9%) with moderate, 3 (7.0%) with mild, and 4 (26.7%) of those who turned out to have no eosinophilia at all. Findings were positive in two children overall (2.2% of those with eosinophilia or 1.19% of total children investigated under ICD code D72.1): a child with moderate eosinophilia was found to be infested with *Enterobius vermicularis*, while another child with severe eosinophilia had *A. lumbricoides* ova in the stool.

Serological testing for *Toxocara* (*T.*) *canis* was performed in 28 children (26.7% of the total or 31.1% of children who actually had eosinophilia): 8 (80.0%) with severe eosinophilia, 10 (27.0%) with moderate eosinophilia, and 10 (23.2%) with mild eosinophilia. Serological evidence of *T. canis* was found in 6 children (5.7% of the total number with ICD code D72.1 or 6.7% of those with actual eosinophilia). Three of the six children with documented *T. canis* infestation had severe eosinophilia (37.5% of those analyzed or 30.0% of the total number in this group), two had moderate eosinophilia (20.0% of those analyzed or 5.4% of group total), and one had mild eosinophilia (10.0% of those analyzed or 2.3% of group total).

Anthelminthic treatment

In total, 56 (53.3%) children received AT: 9 (90.0%) of those with severe eosinophilia, 19 (51.4%) with moderate eosinophilia, 23 (53.5%) with mild eosinophilia, and 5 (33.3%) children with no true eosinophilia. Most of the children were given mebendazole only (42, comprising 40.0% of all children in the series or 79.2% of all treated children): 1 with severe eosinophilia (10.0% of the group total or 11.1% of those treated within the group), 16 with moderate eosinophilia (43.2% of the group total or 84.2%, of those treated within the group), 20 with mild eosinophilia (46.5% of the group total or 87.0%, of those treated within the group), and 5 (33.3% of the group total or 100.0%, of those treated within the group) with no eosinophilia. The remaining 14 children (13.3% of the total or 26.4% of the treated children) were also initially treated with mebendazole but were subsequently shifted to albendazole due to the persistence of eosinophilia. Among those, 8 had severe eosinophilia (80.0% of the group or 88.9% of those treated within the group), 3 had moderate eosinophilia (8.1% of the group or 15.8% of those treated within the group), while 3 had mild eosinophilia (7.0% of the group or 13.0% of those treated within the group).

In all children treated with AT, eosinophilia and other relevant findings (if any) subsided in a matter of a few days to a few weeks after initializing treatment.

Patients with severe eosinophilia

Ten children met the criterion for severe eosinophilia (eosinophils above 5×10^9/L): seven boys and three girls (male:female ratio was 2:3) aged one year and three months to 12 years and two months (median age 9.9 years). The absolute number of blood eosinophils in these children ranged from 5.8 to 62.2×10^9/L (median 11.3×10^9/L). Five of the children had isolated eosinophilia (and were referred to us for this reason), two had gastrointestinal symptoms (abdominal pain, nausea, vomiting, diarrhea), while one had fever and cough, as well as a maculopapular rash apparently triggered by amoxicillin treatment. Another child also had a nonspecific rash, not associated with any other symptoms, while the remaining child had allergic rhinitis. Two children were found to have splenomegaly on initial clinical examination. A stool examination for parasites was performed in all 10 patients and was positive for *A. lumbricoides* in one. A serological test for *T. canis* was performed in eight children, yielding a positive result in three (30.0% of children in the group or 37.5% of those serologically tested). Bone marrow examination was performed in three patients, all three exhibiting a marked hyperplasia of eosinophilic granulocyte lineage.

In addition to the child with parasitologically confirmed *A. lumbricoides* infestation and three children with serologically confirmed toxocariasis, five children were clinically suspected (albeit not confirmed) to also harbor *T. canis*, even though one of these was also found to have IgM antibodies to *Aspergillus* as an alternative explanation for eosinophilia. Two of the five patients in the latter group (suspected helminthiasis without laboratory confirmation) were also genetically investigated for hypereosinophilic syndromes by sequencing an appropriate gene panel. However, no pathological or potentially pathological variants were found.

The child with fever and rash attributed to amoxicillin was diagnosed with an allergic (or pseudoallergic) drug reaction and treated accordingly. All other children with severe eosinophilia received AT: mebendazole alone in the one child known to be infested with *A. lumbricoides* and mebendazole followed by albendazole in the remaining eight children. In all 10 children, eosinophilia resolved upon treatment, and all other signs and symptoms abated, with the exception of persistent splenomegaly in one patient belonging to the group with confirmed toxocariasis.

Discussion

The main limitation of our study design was that it included only patients investigated under the direct diagnostic designation of eosinophilia with the corresponding ICD code. Thus, most or all patients who had been diagnosed with specific disorders featuring eosinophilia were not assigned the code for eosinophilia and were, therefore, not included in this analysis. That probably explains the absence of antineutrophil cytoplasmic antibody-associated vasculitides in our patient series, as well as the near-absence of eosinophilic gastrointestinal disorders in spite of their increasing global prevalence [10]. On the other hand, our choice of inclusion criterion places principal emphasis on the diagnostic workup performed in children with eosinophilia without a readily apparent cause.

The largest subgroup of our patients, comprising over a third of them (35.6%), were children with unexplained eosinophilia that cleared upon AT administered *ex juvantibus*. Allergic disorders (21.1%) were thus not the most prevalent etiological category, contrary to published data, including a recent large (n = 1,178) and well-documented pediatric patient series from Türkiye, where this group of disorders amounted to no less than 80% [11]. However, the prevalence of moderate and severe eosinophilia was much higher among our patients (41.1% vs. 17.8% and 11.1% vs. 1.4%, respectively). Given the approximately tenfold difference in series size, the fact that we discovered no children with a primary immune deficiency is not inconsistent with the recorded prevalence of 8.5% for this group of disorders in the aforementioned study. Allergy/atopy was also the most common cause of hypereosinophilia in a patient review from a tertiary care pediatric center in the United States, followed by graft-versus-host disease, drepanocytosis, and parasitosis [12].

Importantly, no hypereosinophilic syndromes were diagnosed among our patients. This was, admittedly, somewhat unexpected; however, hypereosinophilic syndromes have also been relatively rare in the above-cited study from Türkiye (0.3%) [11] and a Canadian review of one hundred consecutive patients (6.0%) [13], with the *caveat* that the latter included people of all ages. The same applies to a 17-year retrospective review of patient records from Leicester (United Kingdom), where myeloproliferative hypereosinophilic syndromes were found in 2.0% of all patients investigated for eosinophilia [14]. Three of our 10 patients with severe eosinophilia were investigated in this respect by bone marrow examination, yielding only apparently reactive hyperplasia of eosinophilic lineage. Two patients also underwent genetic testing for hypereosinophilic syndromes, with no pathological or suspect gene variants identified. Notably, parasitic etiology was confirmed in four of the 10 children with severe eosinophilia, while in five more the disorder effectively cleared after a course of AT. Only one child had a verified nonparasitological cause of severe eosinophilia (a drug reaction). Such reactions, however, must always be excluded by a thorough anamnesis and clinical examination because they can be severe and even life-threatening, particularly in the event of DRESS [15]. While these findings in no way preclude a comprehensive hematological workup aimed at early detection of hypereosinophilic syndromes in children with severe eosinophilia, the observed outcomes in our series do strengthen the case for making every possible effort to actively seek out potential parasites before proceeding with time-consuming, expensive and partly invasive investigations directed at hypereosinophilic syndromes. This argument may even justify the decision for empirical AT prescribed to our patients.

A rather low number of positive serological or parasitological findings for helminthiasis in our patient series is by no means an unexpected finding. Seroprevalence of *T. canis* in children in Serbia was found to be 10.0% in one study conducted by a group from the University of Niš in collaboration with the "Sapienza" University of Rome [16]. The prevalence was quite similar in a published patient series from Grenoble (6.6% for stool examination and 7.9% for serology) [17], even though this series differed from ours since it included patients of all ages with unexplained eosinophilia. On the other hand, a team from the Croatian National Institute of Public Health led by Sviben found an overall seropositivity rate for *T. canis* of as much as 31% among 142 asymptomatic children with eosinophilia aged 3–18 years [18]. It should be kept in mind, however, that this pertains to a high-risk population and does not necessarily reflect the overall seropositivity rate in Croatia or our region. The local seroprevalence of *T. canis* among children has been positively correlated with the contamination of their peridomiciles – particularly public squares and playgrounds – with parasite ova [19, 20]. It is also associated with a range of socioeconomic factors [21]. A recent study from Texas (United States of America) found that toxocariasis in general, and pediatric toxocariasis in particular, tends to be concentrated in certain epidemiological hotspots [22]. A number of such hotspots have been highlighted in worldwide publications so far, including Ahwaz in Iran [23], the southern seashore of Brazil [24], and Chungcheongnam-do in South Korea [25].

It is conceivable that some of the investigated children without confirmed parasitosis, in reality, harbored undetected parasites, even though this is obviously impossible to prove due to the frequently transient nature of eosinophilia *per se*, as well as the existence of a myriad of potential confounding factors [26]. However, it is reasonably safe to assume that the true incidence of parasite-associated eosinophilia among our patients is higher than that confirmed by parasitological tests since symptoms of such infestation may often be absent, unremarkable, or nonspecific [27]. Furthermore, *Toxocara cati*, a species not covered by currently available serological tests in Serbia, might plausibly account for some of such instances since its prevalence appears to be roughly comparable to that of *T. canis* [28]. It is also impossible to exclude the possibility that some children harbored other rare helminths or protozoa that are not routinely sought. Though all this assuredly speaks of the incomplete adequacy of our currently employed routines for detecting parasites, these results do offer a degree of justification for the practice of administering an *ex juvantibus* course of AT in children with unexplained long-standing eosinophilia. In this regard, it is notable that no adverse effects of such treatment were reported in our series.

Another important takeaway message of the present series is that no standard algorithm or set of guidelines appears to have been consistently employed in the search for the causes of eosinophilia in our institution; indeed, even the very definition of the condition was not applied rigorously, resulting in 15 children being – almost mindbogglingly – incorrectly deemed to have eosinophilia based on their relative eosinophil numbers only. Two-thirds (more precisely 10) of these children received their ICD code D72.1 in a primary healthcare institution, while the remaining (five children) were thus served in our tertiary center. Accordingly, there appears to be significant room

for improvement of existing practices, preferably in the direction of more consistent adherence to appropriate definitions and guidelines, as part of a comprehensive approach, such as that recently proposed by a large collaborative team in France [29].

Conclusion

Pediatric patients with unexplained eosinophilia of all levels of severity require a meticulous and standardized diagnostic approach, including, but not limited to appropriate parasitological investigations. True hypereosinophilic syndromes are rare but need to be carefully excluded. Due to the limited sensitivity of parasitological tests, administration of antihelminthic drugs *ex juvantibus* may be rational in a fraction of children with eosinophilia, particularly in high- or moderate-prevalence areas for *Toxoplasma* species.

Conflict of interest

The authors declare no conflict of interest.

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