The Lack of Association of Eosinophilia and Neurocysticercosis at Clinical Presentation: A Retrospective Analysis of Cases Seen at the National Institutes of Health, 1985–2015

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Abstract. Eosinophilia is a common laboratory finding in helminth infections but whether it is suggestive of neurocysticercosis (NCC) is controversial and inadequately studied. We determined the presence of eosinophilia ($\geq$ 500 eosinophils/mm^3) at clinical presentation in 72 patients with a proven or probable diagnosis of NCC and who had not received corticosteroids within 2 weeks of evaluation and complete blood count. Only two persons whose last possible endemic exposures to NCC were 7 and 6 years earlier had eosinophilia of 500 eosinophils/mm^3 and both had a positive antibody serology to strongyloidiasis. In the one subject where a follow-up assessment was possible, the eosinophilia resolved. The likely cause for eosinophilia in both was strongyloidiasis. Therefore, none of the subjects with newly diagnosed NCC had significant eosinophilia. Eosinophilia in newly diagnosed symptomatic NCC subjects who had remote exposure is unusual and should prompt a search for another process or infection.

INTRODUCTION

Eosinophilia (defined as an absolute eosinophil count $\geq$ 500 eosinophils/mm^3)[1] is commonly associated with helminth infections, but whether neurocysticercosis (NCC), a cestode infection of the brain, is associated with peripheral eosinophilia at clinical presentation is disputed among experts[2] and generally felt too variable to be clinically helpful.[3,4] To determine the association of peripheral eosinophilia and NCC at presentation, a retrospective analysis was performed of 103 confirmed cases of NCC referred to the National Institutes of Health (NIH) for evaluation and treatment between 1985 and January 2015.

METHODS

The studied population included 103 persons with proven or probable NCC enrolled in a NIH, National Institute of Allergy and Infectious Disease protocol, Institutional Review Board approved protocol (85-1-0127) for evaluation and treatment of NCC. All patients signed the protocol consent. The diagnosis of NCC was made on the basis of a combination of features and findings including compatible clinical presentation, history, exposure, diagnostic or compatible magnetic resonance imaging and computed tomography imaging, confirmatory western blot serology for NCC performed by the Centers for Disease Control and Prevention (CDC), presence of serum or cerebrospinal fluid (CSF) cestode antigen, and response to cysticidal treatment and diagnostic or compatible histopathology when available.[5] The earliest available eosinophil count at the time of initial presentation and before treatment was determined from historical records from referring providers, or NIH records. Patients receiving corticosteroids or a recent history of corticosteroid use (within 2 weeks of the evaluation) at the time of first available eosinophil count were excluded from further analysis (31/103, 30%). The case histories of the remaining patients (72) were included in the analysis.

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Medical records were reviewed for the following: geographic exposure history, time since last exposure, type of NCC[2] (parenchymal or extraparenchymal including intraventricular, subarachnoid, and spinal), surgical and medical treatments including past or current antiparasitic medications, and corticosteroid usage. Also, additional testing for infection with other parasites were routinely performed including serologies for *Strongyloides stercoralis* or other parasitic infections as suggested by the history and potential exposures (performed by the CDC). Results of testing for ova and parasites in stool were extracted from referred provider records or obtained as clinically indicated at NIH.

FINDINGS

The characteristics of the study population with and without eosinophilia are summarized in Table 1. Since there are only two persons with eosinophilia and 70 without eosinophilia, a meaningful comparison of the two groups is not possible. Of the total study population, a large majority were immigrants, mostly from Mexico, Central America, and South America. The population had a slight predominance of males, a median age of about 33 years (range: 5–71), and the diagnosis established a median 7 years after migration from an endemic area. Fifty-six of the 72 patients (77.8%) had parenchymal cysts, consisting of 30 (41.7%) with calcifications and 26 (36.1%) with viable or degenerating cysts, and 22.2% had extraparenchymal involvement (ventricular, subarachnoid, or spinal disease).

The two patients with eosinophilia were both immigrants from Central America whose last possible exposures before diagnosis were 6 and 7 years, respectively. One patient presented with multiple parenchymal cysts, and the other with a ventricular cyst. The absolute eosinophil count in each patient before treatment was 500/mm^3. However, both patients had positive serology for strongyloidiasis, a common cause of eosinophilia in immigrant populations.[6–9] Neither had other concurrent diagnoses or illness to account for the presence of eosinophilia. Apart from the treatment of NCC (the patient with the ventricular cyst was treated surgically with cyst resection,

TABLE 1
Characteristics of the study population

Characteristic	Eosinophilic	Noneosinophilic
Number	2	70
Gender	one female/one male	36 (51%) female/34 (49%) male
Age at diagnosis	Range: 26 and 35 years	Range: 5–71 years
	Mean: 30.5 years	Mean: 35 years
Years since last exposure	Range: 6–8 years; mean 7	Range: 1–24; mean: 7
Exposure area	Guatemala/El Salvador	Mexico, Central America, Caribbean: 42
		South America (Peru, Bolivia, Ecuador, Brazil): 13
		Asia (India, Korea, Nepal, Laos): 13
		Africa (Madagascar, Guinea Bissau): 3
		Europe (Romania 1, western Europe 1): 2
Exposure type	Immigrants: 2	Immigrants from endemic areas: 62 (18%)
		U.S. travelers to endemic areas: 10 (14%)
NCC classification	Parenchymal: 1	Parenchymal: 55(79%) (45% calcified)
	Intraventricular: 1	Extraparenchymal: (intraventricular, subarachnoid) 15 (21%)
Eosinophil count	Mean: 500	Mean: 141
Other parasitic diagnoses	Strongyloidiasis (serology): 2	Strongyloidiasis by serology: 2
		Strongyloides larvae in stool: 1
		Schistosomiasis serology positive: 1

and the patient with parenchymal disease was treated with albendazole, corticosteroids, and prophylactic antiepileptic medication), both patients were treated with ivermectin presumptively for strongyloidiasis. Eosinophilia resolved posttreatment in one patient implicating strongyloidiasis as the cause of eosinophilia while the second patient was lost to follow-up and therefore the posttreatment eosinophil level was unobtainable.

DISCUSSION

In this cohort, only two of 72 evaluable patients with NCC had eosinophilia, which appeared to be due to strongyloidiasis, a common cause of occult eosinophilia in immigrant populations.[10] Therefore, eosinophilia could not be ascribed conclusively to NCC in any of our patients given the presence of a concurrent infection known to cause eosinophilia. With the exception of strongyloidiasis, the presence of other helminth gastrointestinal infections, such as ascariasis and hookworm, potentially confounding the association of eosinophilia and NCC was unlikely. First, our patients had resided in the United States for a median of 7 years, a duration of time when most intestinal helminths would have been spontaneously expelled.[11] Second, there is little exposure to gastrointestinal helminths in the United States. On the other hand, eosinophilia in immigrants who are long-term residents of the United States is commonly due to strongyloidiasis.[9–11]

In contrast, patients residing in endemic regions are commonly infected with gastrointestinal parasites including S. stercoralis, confounding the association of NCC and eosinophilia. We could find only one report from Peru, a highly endemic region that suggested peripheral eosinophilia was associated with NCC.[12] But, in that report, the presence of other concomitant helminth infections was not considered. On the other hand, there are a number of reasons that eosinophilia might not be present at clinical presentation of NCC. Symptoms normally occur when the parasite starts to degenerate, which is usually years, if not decades, after exposure and migration of developing stages through the blood stream.[2] It is at the time of migration when peripheral eosinophilia is commonly induced and most profound in other helminth infections.[1] In tissue dwelling parasites such as schistosome

infections, high degrees of eosinophilia commonly occur at the time of the initial migration in naive populations but wanes over time because of host immune modulation.[13] Additionally, in infections with other cestodes that have cystic intermediate stages within the tissues such as *Echinococcus granulosus*, eosinophilia is normally not present even when cysts are viable and sometimes quite large until the cyst ruptures and cyst contents leak out into the tissues.[1,14] Eosinophilia, then, is the hallmark of cyst rupture. Whether eosinophilia commonly occurs as a result of degenerating *Taenia solium* cysts has not been recognized although eosinophils in the CSF is well described in a variable, but usually a minority of patients with extraparenchymal NCC. There are a number of possible reasons why peripheral eosinophilia is not seen despite a significant eosinophilic response in the CSF in some patients (see other parts of the discussion). In addition, these include lack of peripheral cysts that previously degenerated and calcified, sequestration of eosinophilia-inducing parasite antigens within the brain, spine, and CSF, and peripheral cellular tolerance just to mention a few possibilities.

Our cohort differs from endemically residing populations, where there is ongoing exposure and migration of *T. solium* that could possibly incite eosinophilia. However, whether eosinophilia occurs with the usual levels of exposure is unknown, since ingestion and subsequent invasion and migration to the brain and other tissues are clinically silent and seldom recognized. One of us is aware (T. E. Nash, personal communication) of an unpublished case of a participant in a vaccine trial, who was followed prospectively in a heavily endemic area and developed high-level eosinophilia. Subsequently, the patient was diagnosed with disseminated NCC, suggesting that eosinophilia can be elicited during migration and early infection. Induction of eosinophilia during migration through the tissues is not unexpected. Eosinophilia has not been noted in reports of patients diagnosed with disseminated NCC, which would be expected to become clinical apparent when cysts develop minimally 2–3 months (if not longer) after ingestion of ova and migration of onchospheres.[15] In addition, some patients become symptomatic shortly after exposure, a patient group that would not be represented in our cohort.

Another difference in most of our patients is the lack of viable cysts in the muscles and subcutaneous tissues, which

would be expected to be present in an unknown proportion of patient with NCC in endemic populations. Although unproven, it is conceivable that degeneration of muscle/subcutaneous cysts could incite an eosinophilia, particularly in heavy infections. In addition, 30% of our cohort had brain calcifications, almost all with seizures and many with recurrent perilesional edema episodes, a manifestation of NCC that would not be expected to cause peripheral eosinophilia. A larger cohort would have certainly added weight to the results but nevertheless, two-thirds of the patients had viable cysts and many of our patients had extensive disease with viable parasites, and none had eosinophilia.

Despite potential caveats mentioned above, our data indicate that NCC at clinical presentation in patients who present years after exposure is seldom associated with eosinophilia. The presence of eosinophilia in NCC patients should prompt an evaluation for other causes of eosinophilia.

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