琉球大学学術リポジトリ

糞線虫感染時にみられる正常血清免疫グロプリンE値 と末梢血好酸球数に関する研究

メタデータ	言語: en
	出版者: 琉球大学
	公開日: 2017-01-19
	キーワード (Ja):
	キーワード (En): Strongyloides stercoralis, symptom,
	serum IgE levels, HTLV-1, female, elderly
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URL	http://hdl.handle.net/20.500.12000/36045

1	Normal serum IgE levels and eosinophil counts exhibited during Strongyloides
2	stercoralis infection
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34 Abstract

35 Infections with parasites, such as *Strongyloides stercoralis*, typically cause elevated 36 levels of serum immunoglobulin E (IgE) and eosinophils; however, co-infection with 37human T cell lymphotropic virus type 1 (HTLV-1) can cause lower levels of serum IgE 38during S. stercoralis infection. We conducted this study to determine whether serum IgE 39 levels and eosinophil counts could also be related to other patient characteristics or 40 symptoms. Between 1991 and 2014, we measured and compared the symptoms of 237 41 patients and evaluated serum IgE levels and eosinophil counts of 199 patients who 42were infected with S. stercoralis at the Ryukyu University Hospital and the Nishizaki 43Hospital. Medical records were reviewed and blood samples were taken before 44 treatment with the anthelminthic, ivermectin, 2 weeks following the first dosage, and 2 45weeks following the second dosage. Commonly reported symptoms included abdominal 46 pain, diarrhea, and general fatigue. Serum IgE levels were found to be normal in 47patients co-infected with HTLV-1. Additionally, females and patients younger than 70 48years old exhibited normal serum IgE levels when infected with S. stercoralis. No factor 49included in our analysis was found to affect eosinophil counts. Serum IgE levels can 50remain within the normal range for some patients infected with S. stercoralis. Therefore, 51physicians should not eliminate S. stercoralis infection from the differential diagnosis 52solely according to findings of normal or low IgE levels.

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Keywords: *Strongyloides stercoralis;* symptom; serum IgE levels; HTLV-1; female;
elderly.

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57 1. Introduction

58Strongyloides stercoralis is an intestinal nematode and parasite that affects humans 59and is widely distributed in tropical and subtropical regions. Japan's Okinawa Prefecture 60 is located in a subtropical region and, therefore, considered an endemic area for this 61 parasite. In a previous study conducted in Okinawa, we found that the prevalence of S. 62stercoralis infection was 6.3% among a cohort predominantly composed of patients 63 older than 50 years of age (95%) [1–3]. Tanaka et al. reported that the prevalence of S. 64 stercoralis infection was 5.2% in Okinawa [4]. S. stercoralis intestinal infection primarily 65 causes gastrointestinal symptoms. However, one report showed that S. stercoralis 66 infection can also cause rash, cough, and sore throat shortly after infection [5].

67 Asymptomatic patients with *S. stercoralis* infection have been diagnosed by medical

- 68 checkup or a screening test when they are hospitalized in Okinawa. Additionally, 20-
- 69 30% of patients with mild disease have been reported to experience joint pain, low back
- pain, abdominal pain, and numbness [6], while diarrhea, fever, cough, dyspnea, and
- constipation are considered symptoms of severe S. stercoralis infection [7].
- Human T cell lymphotropic virus type 1 (HTLV-1) is an oncogenic retrovirus
- associated with adult T cell leukemia [8, 9]. HTLV-1 has worldwide distribution, but is
- commonly found throughout southwestern Japan, the Caribbean, and some areas of
- 75 Africa and Latin America [10]. Previous reports have established that there is a close
- relationship between *S. stercoralis* and HTLV-1 infections [11–13].
- Generally, serum IgE levels and eosinophil counts are anticipated to be elevated in
- 78 patients with an active parasitic infection (> 170 IU/mL and > 500 cells/µL, respectively).
- 79 However, serum IgE levels and eosinophil counts have been reported at normal levels,
- 80 rather than elevated, in patients co-infected with S. stercoralis and HTLV-1 [14-16].
- 81 Furthermore, a previous study reported that serum IgE levels were low in patients with
- 82 severe S. stercoralis or HTLV-1 co-infection [17]. To our knowledge, previous studies
- 83 have not investigated whether factors other than HTLV-1 infection affect serum IgE

84 levels and eosinophil counts in patients infected with *S. stercoralis*.

- In this study, we closely examine symptomatic and asymptomatic patients infected with *S. stercoralis*, including their characteristics and blood tests results (i.e., serum IgE levels and eosinophil counts). Statistical analyses were conducted to identify which factors, if any, affect serum IgE levels and eosinophil counts in such patients. We also report the symptoms most frequently encountered in patients infected with *S. stercoralis* within our cohort.
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92 2. Materials and Methods

93 2.1 Study population

This study was reviewed and approved by the ethics review board of the Ryukyus University (approval number: 557). Informed consent was waived. Between January 1991 and December 2014, 717 patients were treated for *S. stercoralis* infection at either the Ryukyu University Hospital or the Nishizaki Hospital in Okinawa. All 717 patients were diagnosed, treated, and had confirmed elimination of *S. stercoralis* using the agar plate culture method [18]. All patients were treated with the anthelmintic ivermectin. A single dose of ivermectin (approximately 200 μ g/kg) was administered at the time of confirmed *S. stercoralis* infection, and the same dose was readministered 2 weeks later according to treatment guidelines. This investigation was completed using two separate cohorts. The first cohort (n = 237) was investigated for symptoms. The second cohort (n = 199) was investigated for serum IgE levels and eosinophil counts. Patients (n = 480) that did not complete the entire series of interviews were excluded. A subset of patients from the first cohort (n = 38) were excluded because of a lack of complete blood testing.

108 2.2 Patient interviews

109 Patients were interviewed about various symptoms, including presence of abdominal 110 pain, diarrhea, pruritus, general fatigue, appetite loss, nausea, constipation, vertigo, 111 heart burn, vomiting, rash, headache, cough, numbness, blurred vision, muscle pain, 112arthralgia, lumbago, frequent urination, and fever. Patient experience for each variable 113 was graded using an ordinal Likert-type scale: 0 = no symptoms; 1 = mild, symptoms 114 are easily tolerated; 2 = moderate, symptoms are sufficient to cause interference with 115normal activities; or 3 = severe, symptoms prohibit the performance of normal activities. 116 Patient interviews were conducted before treatment (D_0) , 2 weeks following the first 117 dosage (D_{14}) , and 2 weeks following the second dosage (D_{28}) . 118

119 2.3 Blood testing

120Blood samples were tested for serum IgE levels and eosinophil counts before121treatment and after each administration of ivermectin. In our analysis, we defined serum

- 122 IgE levels >170 IU/mL and peripheral eosinophil counts \geq 500 cells/µL as elevated.
- 123

124 2.4 Statistical analyses

125One-way ANOVA was used to compare the scores of symptoms before and after 126 treatment. Spearman's non-parametric correlation coefficient, p, was used to 127investigate the correlation between serum IgE levels or eosinophil counts and age, 128because age was not normally distributed. Patient age was changed from a continuous 129scale to a binary category (<70 years old or ≥70 years old). A multiple logistic regression 130 model yielding odds ratios (ORs) and 95% confidence intervals (CIs) was used to 131 identify factors that were significantly associated with serum IgE levels or eosinophil 132counts. ANOVA analysis was used to analyze the difference in serum IgE levels and 133 eosinophil counts among groups. Cohorts were divided by sex, age (<70 years old or

134 \geq 70 years old), and HTLV-1 status.

135 All statistical analyses were conducted using the SPSS (version 21.0) software

- 136 package, and P-values reported were two-sided.
- 137

138 3. Results

139 3.1 Patient Characteristics

140 The mean age of the first cohort was 63.47 years, approximately 70% was male, and

141 28.2% was co-infected with HTLV-1. The mean age of the second cohort was 62.39

142 years, approximately 70% was male, and 40.7% was co-infected with HTLV-1. There

143 were no significant differences between the two cohorts (Table 1).

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145 Table 2 shows a comparison of symptom scores on D₀, D₁₄, and D₂₈. The symptom

146 scores for abdominal pain, diarrhea, and general fatigue were all significantly improved

147 after treatment with ivermectin (p < 0.01 for all). The scores of other symptoms,

148 although trending toward improvement following ivermectin treatment, were not

- significantly different.
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151 3.2 Investigation of factors affecting serum IgE levels

152Figure 1 shows the correlation between serum IgE levels and age. A positive direct 153correlation was observed overall between serum IgE levels and age ($\rho = 0.22$, p < 0.01, 154n = 199). A significantly positive correlation was also observed between serum IgE 155levels and age in HTLV-1 negative patients ($\rho = 0.24$, $\rho < 0.01$, n = 118) and male 156patients without HTLV-1 infection ($\rho = 0.32$, p < 0.01, n = 86). A slightly positive 157correlation was also observed between serum IgE levels and age in female patients 158without HTLV-1 infection ($\rho = 0.21$, p = 0.05, n = 32). However, this correlation was not 159observed in HTLV-1 positive patients ($\rho = 0.18$, p = 0.10, n = 81). This correlation was 160 confirmed in logistic regression analyses, which showed that patients who were female, 161 younger than 70 years old, had normal eosinophil counts, or were co-infected with 162 HTLV-1 were more likely to present with normal serum IgE levels (p < 0.01 for all) (Table 163 3). 164 Figure 2 shows the comparison of serum IgE among four distinct sex and age

165 categories. Serum IgE levels were significantly elevated in all patients \geq 70 years old (*p*

166 < 0.01). Furthermore, serum IgE levels were considerably lower in female patients <70 167 years old (p < 0.01), suggesting a synergistic effect of these two variables. Table 5A 168 shows the evaluation of potential relationships between sex-age categories and serum 169 IgE levels in patients co-infected with HTLV-1. Serum IgE levels were significantly 170elevated in all patients \geq 70 years old (p < 0.01). Furthermore, serum IgE levels were 171 considerably lower in female patients <70 years old (p < 0.01), suggesting a synergistic 172effect of these two variables. Table 5B shows the evaluation of potential relationships 173 between sex-age categories and serum IgE levels in patients without HTLV-1 infection. 174Both serum IgE levels and eosinophil counts were affected by sex and age in patients 175without HTLV-1 infection.

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177 3.3 Investigation of factors affecting eosinophil counts in systemic blood

178Figure 3 shows the correlation between eosinophil counts and age. A slightly positive 179 correlation was observed overall between eosinophil counts and age ($\rho = 0.19$, p < 0.01, 180 n = 199). A significantly positive correlation was also observed between eosinophil 181 counts and age in HTLV-1 negative patients ($\rho = 0.23$, p < 0.05, n = 118) and male 182 patients without HTLV-1 infection ($\rho = 0.32$, $\rho < 0.01$, n = 86). A slightly positive 183 correlation was also observed between eosinophil counts and age in female patients 184 without HTLV-1 infection ($\rho = 0.14$, p < 0.05, n = 32). However, this correlation was not 185 observed in HTLV-1 positive patients ($\rho = 0.10$, p = 0.37, n = 81). Interestingly, only 186 patients with normal IgE levels were likely to have low eosinophil counts in the blood 187 serum (p < 0.05) (Table 4).

188 Figure 4 shows the comparison of eosinophil counts among four distinct sex and age 189 categories. Similar trends to those observed for serum IgE levels were observed, likely 190 because serum IgE levels are dependent on eosinophil counts. In particular, males and 191 patients \geq 70 years of age exhibited significantly higher eosinophil counts than any other 192 group (p < 0.05 for each). Table 5A shows the evaluation of potential relationships 193 between sex-age categories and eosinophil counts in patients co-infected with HTLV-1. 194 Eosinophil counts were not affected by sex or age (p = 0.84). Table 5B shows the 195 evaluation of potential relationships between sex-age categories and eosinophil counts 196 in patients without HTLV-1 infection. Eosinophil counts were significantly elevated in all 197 patients \geq 70 years old (p < 0.01). Furthermore, serum IgE levels were considerably 198lower in female patients <70 years old (p <0.01).

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200 4. Discussion

201S. stercoralis intestinal infection typically causes gastrointestinal symptoms. Our 202 study showed that abdominal pain, diarrhea, and general fatigue were improved after 203ivermectin treatment. Tanaka reported that S. stercoralis can also cause rash, cough, 204and sore throat immediately after infection [5], and Tsai et al. reported that diarrhea, 205fever, abdominal pain, cough, dyspnea, and constipation were symptoms of severe S. 206 stercoralis infection [7]. Despite this documentation, we did not observe such symptoms. 207 A potential explanation for this difference may be that subjects in our cohort only 208suffered from mild infection, and hospitalized patients with severe S. stercoralis 209 infection were not included.

210In agreement with previous studies [1, 16], our results also showed that serum IgE 211levels were normal in patients co-infected with S. stercoralis and HTLV-1. Porto et al. 212reported that HTLV-1 infection decreases Th2 type immune responses, and this same 213mechanism is likely responsible for the lower serum IgE levels in co-infected patients 214[16]. Our study, however, showed that eosinophil counts of HTLV-1 positive patients 215were not significantly different from that of HTLV-1 negative patients. Although this 216information is not novel based on Th2 pathway improvements [19], the mechanism of 217IgE production and the crosstalk between eosinophils and Th2 lymphocytes remains 218unclear.

219To our knowledge, this is the first report to describe a relationship between sex and 220serum IgE levels in patients infected with S. stercoralis. However, other studies have 221reported a similar relationship among female patients with bronchial asthma and 222allergies [20] and in umbilical cord blood IgE levels [21]. Hunninghake et al. reported 223variations in IgE levels among asthmatics. Increased transcription of the interleukin-17 224receptor B gene was found to increase IgE levels in males. However, a significant 225correlation between gene transcript abundance and serum IgE levels was not found in 226females [22]. To our knowledge, no other studies investigating the correlation between 227serum IgE levels and IL-17RB in asthmatics have been conducted, nor have any other 228reports compared serum IgE levels between males and females with helminth 229 infections.

Our study also found that as age may affect serum IgE levels. Patients younger than
70 years of age frequently present with normal IgE levels, rather than anticipated

elevated levels. Mutapi et al. also reported a positive correlation between serum IgE
levels and age in patients infected with *Schistosoma mansoni* [23]. Here, we speculate
that the age–antibody relationship might be caused by the increased duration of
parasitic infection. However, there were no significant correlations between serum IgE
levels and age in females or HTLV-1 co-infected patients. These results further suggest
that female sex and HTLV-1 are inhibitive factors on serum IgE levels in *S. stercoralis*infection.

We speculated that serum IgE levels are dependent on eosinophil counts, and similar results were observed in univariate analyses. In previous studies [15, 16], eosinophil counts were found to be decreased in patients co-infected with *S. stercoralis* and HTLV-1. The statistical analyses used and inherent cohort differences may explain the

243 differences between our results and that of previous studies.

There are some limitations associated with this study. It is well known that allergies,

immunosuppressants, steroid use, human immunodeficiency virus infection, and other
 parasitic infections can also affect serum IgE levels and eosinophil counts.

- 247 Unfortunately, these confounders were not included in the survey and, thus, their effects248 could not be analyzed.
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250 5. Conclusions

251 Our study showed that serum IgE levels were normal, rather than elevated as is 252 typical during parasitic infections, in *S. stercoralis*-infected patients who were female, 253 younger than 70 years, or co-infected with HTLV-1. Therefore, physicians should not 254 eliminate *S. stercoralis* infection from the differential diagnosis solely according to 255 findings of normal or low serum IgE levels. Mechanisms regulating IgE, eosinophils, and 256 Th2 antihelminthic responses need further research.

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258 6. Acknowledgements

This research did not receive any specific grant from funding agencies in the public,commercial, or not-for-profit sectors.

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262 7. Conflict of Interest Statement

263 The authors declare that there are no conflicts of interest.

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