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The relation between immunocompromised status and *Strongyloides stercoralis* infection: case-control study

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Abstract. *Strongyloides stercoralis* infection is caused by intestinal nematodes in the human body, which in immunocompromised individual, may cause severe morbidity and fatality. This study aimed to reveal the current prevalence of *S. stercoralis* infection among the stool samples sent to Parasitology Laboratory FMUI and identify its association with the status of immunocompromised. A case-control study with consecutive sampling method was, conducted between March-June 2013. Subjects were the patients of hospitals/laboratory who sent their stool samples to the Parasitology laboratory of FMUI. All stools were examined through direct examination, followed by Harada-mori culture. The immune status of the patients was identified through their medical records. The total number of stools collected was 170 consisted of 108 males and 62 females. The age of the patients ranged from 2 to 80 years old (average 33.41±22.65 years); 18.2% (31/170) was immunocompromised and 81.8% (139/170) was immunocompetent. A total of 18/170 (10.6%) stools were positive of *S. stercoralis* larvae; 6 stools (19.4%, 6/31) were from the immunocompromised and 12 stools (8.6%, 12/139) originated from the immunocompetent. The result suggested that immunocompromised status has a positive relation towards *S. stercoralis* infection. Results from this study could serve as input for clinicians for better management of cases with diarrhoea, especially among the immunocompromised.

INTRODUCTION

Strongyloides stercoralis is a nematode of human small intestine, which could be transmitted through soil as well as has autoinfection life cycle. *Strongyloides* is widely spread globally in countries with tropical and subtropical climate which is suitable for the growth of *S. stercoralis* eggs and larvae (Siddiqui *et al*., 2011).

Indonesia is a tropical country at equator line, making its tropical climate a suitable environment for *S. stercorlis* infection. However, there were very few reports on the prevalence of *S. stercoralis*. Widjana *et al.*, 2001 reported a prevalence of *S. stercoralis* of 1.6% among the people of Bali, and 2-3% in Surabaya. *Strongyloides stercoralis* infection usually occurs in tropical areas with high humidity, low hygiene and sanitation, especially in endemic areas. Human beings are the main host of *S. stercoralis* infection, while dogs, cats and other mammals act as the reservoir hosts (Grove, 1996).

Most strongyloides infections are asymptomatic in immuncompetent individuals, so it is categorized as opportunistic infection which will cause clinical symptoms in immunocompromised individuals (Ramanathan & Nutman, 2008). The status of immunocompromised is a risk factor related to *S. stercoralis* infection. Grove, 1996 stated that *S. stercoralis* infection could become severe (hyperinfection), among the immunocompromised such as the use of immunosuppressant (long term corticosteroid, lymphoma, Human T cell Lymphotropic

virus infection, organ transplantation), malnutrition and HIV/AIDS.

Corticosteroids could increase apoptosis activity in TH-2 cell. Corticosteroid along with cortisol work on a specific receptor known as glucocorticoid receptor (GCRs) found on the $CD4^+$ of TH-2 cell membrane which could increase apoptosis and dysfunction of TH-2-cell and inhibit proliferation of eosinophil. The decreased number of eosinophil in human body will obstruct response of the mast cells which could cause hyperinfection (Vadlamudi *et al.*, 2006; Siddiqui *et al.*, 2011). Corticosteroid also increases the level of ecdysteroid as a signal which would accelerate the development of eggs into larva, and intensify the autoinfection process which will develop into a hyperinfection syndrome and strongyloidiasis diseminata (Vadlamudi *et al.*, 2006; Siddiqui *et al.*, 2011). Signs and symptoms from patients with long term use of corticosteroid have begun as early as 20 days after the onset of steroid therapy and as late as several years without an apparent additional immunocompromising condition appearing (Keiser & Nutman, 2012).

HIV/AIDS is one of the causes of immunocompromised condition which bears the risk of developing hyperinfection of *S. stercoralis*. In HIV infection, cellular immunodeficiency occurs due to a progressive decline in CD4 + T-lymphocytes. $CD4^+$ antigen is found in 20% of macrophages, 10% in monocytes and 5% in B-lymphocytes, and functions in both Th-1 and Th-2 cells. If HIV virus attacks $CD4^+$ of T cell, it will impair the macrophage function which subsequently will decrease synthesis of Th1 cytokines while increasing the synthesis of Th2 cytokines and also inhibit B cells and T-lymphocytes cytolysis differentiation. During *S. stercoralis* infection, IFN-γ and IL-10 increase, along with the decrease of IL-4, IL-5 and IgE and the transformation of predominant Th-2 response into the Th-1 response (Bogitsh *et al.*, 2013).

Meanwhile, malnutrition is also an individual's condition and may cause immunocompromised state with the risk of hyperinfection. This is due to intestinal mucosa disorders, causing the host unable to remove the worms. During this condition, a disorder known as Protein Energy Malnutrition (PEM) develops, causing impairment of cellular immunity, phagocytic function of the complement system, and also affect the production of antibody and cytokine which could contribute to *S. stercoralis* hyperinfection (Peters *et al.*, 2009).

Strongyloidiasis research reported in Indonesia was generally community-based. There has been hardly any recent *Strongyloides* research conducted from samples in hospitals. Research with case-control design would allow us to conduct studies in hospitals or among the community. Both community and hospital have their own advantages and benefits. Therefore, research is needed to ensure the number of cases of *S. stercoralis* infection among patients from hospitals, outpatient care and laboratory referrals and to identify the relationship of immunocompromised status towards *S. stercoralis* infection.

MATERIALS AND METHODS

This was an analytical observational study with a case-control design to see the effect of immunocompromised condition towards *S. stercoralis* infection. Case was obtained from samples positive for *S. stercoralis* while the negative ones were regarded as control. The samples were patients whose stools were submitted between March-June 2013 to Parasitology Laboratory, Faculty of Medicine, Universitas Indonesia. Samples were selected through consecutive sampling following inclusion and exclusion criteria. The minimum number of samples for the case and control was 163. The inclusion criteria was: subjects must be at least 2 years of age, with soft or watery stool, or had a record of soft/watery stool for the last three months. The exclusion criteria was incomplete data, insufficient amount of stool (<0.5g), stool kept in refrigerator.

Parasitology examination to diagnose *Strongyloides* infection consisted of fresh stool examination on wet mount, followed by Harada-mori culture (Kosin *et al.*, 1973) on all stools which fitted the study criteria. To

determine whether a subject was immunocompromised or immunocompetent, the medical records were used as consideration. Data analysis was performed using SPSS v11.5 software.

RESULTS

A total of 202 subjects (patients) submitted their stool specimens to Parasitology laboratory between March-June, 2013 and 170 subjects met the study criteria. Most of the subjects were male, aged 2–80 years old (average of 33.1 years, SD 26.7). There were 18/170 (10.6%) individuals positive for *S. stercoralis* and 31/170 (18.2%) with immunocompromised state (Table 1). The distribution of immunocompromised state (31 patients) were as follow: 22 individuals were HIV, 7 individuals with long term use of corticosteroids and 2 individuals were suffering from malignancy (Table 3).

We found 19.4% (6/31) immunocompromised patient positive for *S. stercoralis* infection, while 8.6% (12/139) was immunocompetent (Table 2). The immunocompromised patients who were positive for *S. stercoralis* infection were caused by HIV (4 individuals) and long term use of corticosteroids (2 individuals) (Table 3).

The statistical analysis with Fisher exact test showed no association between *S. stercoralis* infection with immunocompromised status (p=0.085, p>0.05, CI 0.871 – 7.403), OR value =2.54.

Table 1. Characteristic of Population

	n	percentage
Gender		
Male	108	63,5
Female	62	36,5
Strongyloides stercoralis Infection		
Positive	18	10,6
Negative	152	89,4
Immunocompromised State		
Positive	31	18,2
Negative	139	81,8

Table 2. *S. stercoralis* infection and the immune status

S. stercoralis infection	Immunocompromised State		Total
	Positive	Negative	
Positive	6	12	18
Percentage in Immunocompromised State	19,4%	8,6%	
Percentage of total	3,5%	7,1%	10,6%
Negative	25	127	152
Percentage in Immunocompromised State	80,6%	91,4%	
Percentage of Total	14,7%	74,7%	89,4%
Total	31	139	170
	18,2%	81,8%	100%

Table 3. Immunocompromised condition associated with *S. stercoralis* infection

Immunocompromised condition	*S. stercoralis infection*		Total
	Positive	Negative	
HIV	4	18	22
Percentage in immunocompromised state	18.2%	81.8%	100%
Long term users of Corticosteroids	2	5	7
Percentage in immunocompromised state	28.6%	71.4%	100%
Malignancy	0	2	2
Persentage in immunocompromised state	0%	100%	100%
Total	6	25	31
	19.4%	80.6%	100%

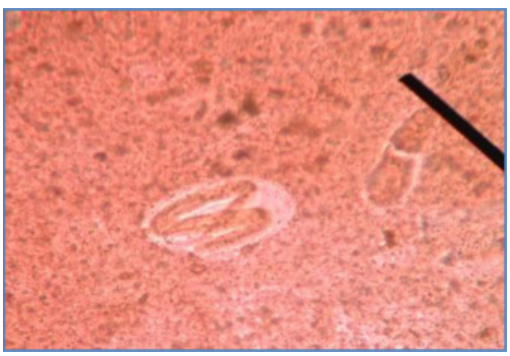

Figure 1. Egg of *S. stercoralis* in eosin staining direct examination

Figure 2. *S. stercoralis* filariform larva in lugol staining from patient's sputum after harada mori

There was only one patient with hyper-infection. We found rhabditiform larva and eggs from the stool (Figure 2) and larva from the sputum (Figure 1).

DISCUSSION

There is hardly any report on *Strongyloides* prevalence in Indonesia in the last 20 years in contrast to reports on STH. As it is not easy to recognize cases with *Strongyloides* infection as well as its capability to live dormant for many years in human body, makes this infection underdiagnosed. In this study, it was shown that the prevalence of *Strongyloides* among the stool specimens sent to Parasitology laboratory was 10.6 %. This result was higher than previous reports of *Strongyloides* infection in Bali (1.6%; Widjana & Sutisna, 2001) and in Surabaya (2%; Buditjahjono,1995). A survey of *S. stercoralis* infection conducted among a community in Halmahera in 1991 gave prevalence of 4.4% (Mangali *et al.*, 1994). Our result was also higher than similar studies conducted in Phramongkutklao Bangkok Hospital, Thailand where the prevalence of *S. stercoralis* infection was 6.7% (Ananthaphruti *et al.*, 2000). Interestingly, in South-East Asia, a highly endemic part of the world, several countries report infection rates within a comparably small range 17.5% to 26.2% (Schar *et al.*, 2013).

Based on our study, it was found that the *S. stercoralis* infection affects more men than women. This may be due to the number of samples which consisted of more male patients than female patients. However, if the number of female patients was compared to the total number of women and the same was

applied to male patients, the prevalence between female and male patients were almost the same. This is similar to the result reported by Azira *et al*. (2013) in a study conducted in a teaching hospital in Kelantan Malaysia where patients with *S. stercoralis* positive were mostly male. However, it was different from the results in Bali where more women were positive with *S. stercoralis* (Widjana & Sutisna, 2001).

Subjects with immunocompromised status emerged from 31 people comprising 22 people infected with HIV, seven long term users of corticosteroids, and two people with malignancy. *Strongyloides stercoralis* infections were found in six immunocompromised patients with four (18.2%, 4/22) suffering from HIV/AIDS. It showed a higher result than it was in Ethiopia which reported 9% cases of *S. stercoralis* infection in HIV/AIDS patients (Mekonnen *et al*., 2001). However, these results were still relatively lower compared to studies conducted in Thailand which reported a percentage of 22% of *S. stercoralis* infection in HIV/AIDS patients (Tomanaken *et al*., 1999) and studies in Hong Kong which reported that 86% (6/7) had a record of long term users of corticosteroid. While *S. stercoralis* infection among patients with immunocompromised status caused by long-term use of corticosteroid, only consisted of two people (28.6%, 2/7). This was fairly higher than the proportion of *S. stercoralis* infection caused by HIV/AIDS (18.2%) and has almost the same result as the study reported by Asdamongkol *et al*., (2006) where the proportion of *S. stercoralis* infection in immunocompromised patients were mostly caused by long term use of corticosteroids.

In this research, from two immunocompromised patients caused by long term used of corticosteroid since January 2013, there was only one patient who developed hyperinfection and strongyloidiasis dissemination. Clinical manifestations experienced by the patient were chronic coughs, chronic diarrhoea, and hypereosinophilia since January 2013. During treatment, patient was diagnosed with peritoneal tuberculosis and bronchopneumonia. Hyperinfection and strongyloidiasis dissemination were both manifested by the *S. stercoralis* larva found in the sputum (Figure 1). Hyperinfection state could be due to corticosteroid as it increased the level of ecdysteroid in the human body. This substance functioned as a signal, which accelerated the development of eggs into a larvae and thus intensified the autoinfection process that would develop into a hyperinfection syndrome and strongyloidiasis diseminata (Vadlamudi *et al*., 2006; Siddiqui *et al*., 2011).

In this study, subjects with positive *S. stercoralis* infection and having immunocompromised status were six (19.4%, 6/31) patients while subjects with immunocompetent status were 12 (8.6%, 12/139) patients. Risk of having *S. stercoralis* infection immunocompromised individuals compared to individuals with immunocompetent status was within the following odds ratio (OR): 2.54 (95% CI: 0,871 – 7,043), with a P-value of 0.082. This indicated that risk factor of immunocompromised status has a positive relation towards *S. stercoralis* infection even though statistically insignificant (P >0.05) and CI >1. Statistically, the insignificant result of this study might be caused by many factors, such as number of cases obtained were still insufficient due to the limited time of research, patients with immunocompromised status were not exposed to *S. stercoralis* infection, and almost all patients who came to the parasitology laboratory of FMUI were from urban areas with different levels of endemic and small probability of being infected by *S. stercoralis*. Meanwhile, infections caused by this type of worm were more commonly found in rural areas and in a society with lower socio-economic status (Grove, 1996; Keiser & Nutman, 2004; Siddiqui *et al*., 2011). Nevertheless, the number of *S. stercoralis* was still fairly high. This provides information for clinicians who can use this for policy making to improve infection management in complaints of diarrhoea, especially from the patients with immunocompromised condition.

This research could be improved by extending time of research in order to fulfil the minimum number of cases. Future studies

should ensure sample selection be carried out in areas with same environmental conditions.

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