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Correlation between *Toxoplasma gondii* and *Cytomegalovirus* infections and somatic symptom in community

Isti Anindya[1]*, Budi Mulyono[2], Carla R. Marchira[3], Marsetyawan HNE Soesatyo[4]

[1]Study Program of Master in Biomedical Sciences, [2]Department of Clinical Pathology, [3]Department of Psychiatry, [4]Department of Histology and Cell Biology, Faculty of Medicine, Universitas Gadjah Mada, Yogyakarta

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ABSTRACT

The prevalence of *Toxoplasma gondii* and *Cytomegalovirus* (CMV) infections are high in the world. Indonesia is one of the countries with high prevalence of these infections varied from 20 to 63%. The *T. gondii* and CMV infections infections can be chronic and cause maternal and fetal deatht as well as infant defects. Previous clinical study reported that chronic infections can cause somatic symptoms indicating psychological stress. The aim of this study was to evaluate the correlation between *T. gondii* and CMV infections with somatic symptoms. This was an observational study with a cross sectional design involving 103 eligible patients with seropositive IgG *T. gondii* or and CMV from six cities in Java, Indonesia. The presence of somatic symptoms was detected by using somatic symptoms inventory (SSI) questionnaire. Logistic regression analysis was used to evaluate the correlation. The percentage of patients with somatic symptoms (SSI score >48) in seropositive groups of IgG anti-*T. gondii,* anti-CMV, anti-*T. gondii* and CMV were 70.0; 62.2 and 36.2%, respectively. In addition, the prevalence ratio (PR) for each group were 1.333, 1.178, and 0.954, respectively. No significantly different in PR was observed in this study ($p>0.05$). In conclusion, the *T. gondii* and CMV infections are not correlted with the somatic symptoms.

ABSTRAK

Prevalensi infeksi *Toxoplasma gondii* dan *Cytomegalovirus* (CMV) tinggi di dunia. Indonesia merupakan salah satu negara di dunia dengan prevalensi yang tinggi akibat infeksi *T. gondii* dan CMV ini dengan prevalensi bervariasi antara 20 sampai 60%. Infeksi *T. gondii* dan CMV dapat menjadi penyakit kronik dan menyebabkan kematian ibu dan anak serta kecacatan pada anak yang dilahirkan. Pada penelitian klinik yag dilakukan sebelumnya dilaporkan infeksi kronik dapat menyebabkan gejala somatik yang mengindikasikan adanya stres psikologi. Penelitian ini bertujuan untuk mengkaji hubungan antara infeksi *T. gondii* dan CMV dengan gejala somatik. Penelitian ini merupakan penelitian observasional dengan rancangan potong lintang yang melibatkan 103 penderita dengan infeksi *T. gondii* dan CMV dari enam kota di Jawa, Indonesia. Adanya gejala somatik dideteksi menggunakan kuesionair *somatic symptoms inventory* (SSI). Analisis regresi logistik digunakan untuk mengkaji adanya hubungan infeksi *T. gondii* dan CMV dengan gejala somatik. Persentase pasien dengan gejala somatik (skor SSI >48) pada kelompok seropositif IgG anti-*T. gondii*, anti-CMV, anti-*T. gondii* dan anti-CMV berturut-turut adalah 70,0; 62.2 dan 36,2%. Selanjutnya rasio prevalensi (RP) untuk masing-masing kelompok

* corresponding author : istianindya@gmail.com

berturut-turut adalah 1,333; 1,178 dan 0,954. Tidak ada perbedaan bermakna dalam RP dari hasil penelitian ini ($p > 0.05$). Dapat disimpulkan infeksi *T. gondii* dan CMV tidak berhubungan dengan gejala somatik.

Keywords: *Toxoplasma gondii* - cytomegalovirus – chronic infections - somatic symptom - stress

INTRODUCTION

Toxoplasma gondii is one of the most parasites found in human that cause the disease known as toxoplasmosis. Toxoplasmoxis is present in all countrie in the world with serelogical positive rate varies between less than 10 to over 90%.[1-3] In Indonesia the toxoplasmosis prevalence also varies between 20 to 60%. Yogyakarta Special Region is the second city with highest toxoplasmosis prevalence (51%) after Surabaya, East Java (61%).[4] Toxoplasma gondii can cause birth defect. In a pregnant women with toxoplasmosis, the *T. gondii* can cross the placenta from mother to the baby with sometimes catastrophic consequences. Children born with congenital toxoplasmosis can have classical symptoms of hydrocephalus, retinochoroiditis and encephalitis.[1]

The *Cytomegalovirus* (CMV) is one of the most common opportunistic pathogens found in immunocompromised patients.[5] Smith and Rowe in 1956 and Weller in 1957 independently isolated virus strains in human blood and suggested the term *"Cytomegalovirus"* for the virus that was also found in infant urine.[6] The prevalence of CMV infection in the world in 2009 reached ≥70% for the countries with bad infection management and 50-70% for those with some blood infection management. The prevalence of CMV infection in Indonesia in 2004 reached 87.8%.[7]The chronic infection such as *T. gondii* and CMV can cause psychological stress such as depression. Markovitz *et al*.[8] reported that individuals with seropositive of *T. gondii* had more than twice as high risk of depression compared to those with seronegative. In addition Goebel *et al.*[9] reported that patients with seropositive IgG anti-CMV have higher risk of depression. The depression is associated with somatic symptoms. Somatic symptoms including anxiousness and fatigue are a common feature in patients with depression.[10] This study was conducted to evaluate the correlation between *T. gondii* and CMV infections with somatic symptom in community setting.

MATERIALS AND METHODS

Subjects

This was an observational study with cros sectional design involving people who suspected *T. gondii* and CMV infections from six cities in Java including Bogor and Bandung West Java, Yogyakarta Special Region, Semarang Central Java, Malang and Surabaya East Java. The study was conducted over a period of one month (February 6th to March 5th) in collaboration with Indonesia Aquatreat Therapy Foundation. The *T. gondii* infection was diagnosed based on IgG anti-*T. gondii* examination, whereas the CMV infection based on IgG anti-CMV examination. Protocol of the study was approved by the Medical and Health Research Ethics Committee of the Faculty of Medicine of Universitas Gadjah Mada, Yogyakarta (Number KE/FK/156/EC/2016).

Protocol of study

On the day that has been agreed, patients with *T. gondii* and CMV infetions in each city were gathered to be selected. Data of the patients were obtained from the Indonesia Aquatreat Therapy Foundation. An explanation concerning background, objectives and benefit of the study was given. Patients who met the inclusion and exclusion criteria were given an informed consent to be signed. The inclusion criteria were patients with the seropositive IgG anti *T. gondii,* and IgG anti-CMV in just examination. The exclusion criteria were the patients with more than one IgG anti *T. gondii* and IgG anti-CMV examinations or underwent treatment and the IgG anti *T. gondii* and IgG anti-CMV examinations were not standard. Selected patients were then grouped into three groups i.e. patients with just the seropositive IgG anti *T. gondii* (Group 1), patients with just the seropositive IgG anti-CMV (Group 2) and patients with both the seropositive IgG anti *T. gondii,* and IgG anti-CMV (Group 3). All selected patients were given somatic symptoms inventory-24 (SSI-24) questionnaire to be filled under supervison of the research assistants.[11] Patients without the somatic symptoms were considered if the SSI score ≤ 48 and patients with the somatic symptoms if the SSI score > 48.

Statistical analysis

Data were presented as frequency or percentage or mean ± standard deviation (SD). Logistic regression analysis was applied to calculate the prevalence ration (PR) which was used to evaluate the correlation between the *T. gondii* and CMV infections with the level of the somatic symptom. A p value less than 0.05 was considered significant.

RESULTS

The study was conducted over a period of one month (February 6th to March 5th, 2016) with 177 selected subjects and 103 eligible subjects. The characteristics of subjects were presented on TABLE 1. The mean age of subjects ranged between 32 and 33 years with most of them were females (82%). All most participants were married (98%) and graduated from university (56%). The most occupations of subjects were housewives (41%), whereas the most of subjects had income between IDR 1-3 millions. The majority of subjects came from Central Java (46%) and most of them experienced somatic symptoms at medium to high levels (SSI score > 48).

TABLE 1. Characteristics of subject in each group

Characteristics	Group 1 (n=30)	Group 2 (n=37)	Group 3 (n=36)
Age (mean ± SD years)	32.5 ± 6.0	30.5 ± 6.3	33.3 ± 7.4
Sex [n (/%)]			
• Female	27 (90)	28 (76)	28 (80)
• Male	3 (10)	9 (24)	7 (20)
Marital status [n (/%)]			
• Married	29 (97)	36 (97)	36 (100)
• Non-married	1 (3)	1 (3)	0
Education [n (/%)]			
• Postgraduate	0	0	1 (3)
• Graduate	17 (57)	22 (60)	19 (52)
• Undergraduate	4 (13)	0	1 (3)
• Senior high school	7 (23)	13 (34)	15 (42)
• Junior high school	2 (7)	1 (3)	0
• Elementary school	0	1 (3)	0
Occupation [n (/%)]			
• Government employee	7 (23)	16 (43)	13 (37)
• Entrepreneurs	2 (7)	7 (19)	7 (18)
• Housewives	16 (54)	13 (35)	13 (37)
• Educators	4 (13)	1 (3)	2 (6)
• Health professionals	1 (3)	0	1 (3)
Income (IDR) [n (/%)]			
• > 12 million	2 (7)	1 (3)	0
• 8-12 million	1 (3)	2 (5)	2 (5)
• 5->8 million	2 (7)	1 (3)	2 (5)
• 3->5 million	6 (20)	12 (32)	10 (28)
• 1->3 million	15 (50)	18 (49)	19 (53)
• <1 million	4 (15)	3 (8)	3 (9)
Domicile [n (/%)]			
• West Java	14 (47)	14 (38)	10 (30)
• Central Java	8 (27)	17 (46)	23 (64)
• East Java	8 (27)	6 (16)	2 (6)
Somatic symptoms factor [n(/%)]			
• SSI score ≤ 48	9 (30)	14 (38)	23 (64)
• SSI score > 48	21 (70)	23 (62)	13 (36)

The PR of somatic symptoms in each group was presented in TABLE 2. No significantly different in PR of somatic symptoms was observed in each group ($p>0.05$). It was indicated that the IgG anti-*T. gondii* levels (Group 1) and IgG anti-CMV levels (Group 2) or both (Group 3) were not correlated with somatic symptoms.

TABLE 2. The PR of somatic symptoms in each group

Characteristic	Group 1		Group 2		Group 3	
	Prevalence Ratio (95% CI)	p	Prevalence Ratio (95% CI)	p	Prevalence Ratio (95% CI)	p
IgG Level						
• Medium to High	1.333 (0.410)	0.625	1.178 (0.419)	0.748	0.954 (0.411)	0.916
• Low	1.000 (Reference)	-	1.000 (Reference)	-	1.00 (Reference)	-
Sex						
• Female	0.888 (0.161)	0.894	1.928 (0.528)	0.266	0.868 (0.503)	0.643
• Male	1.000 (Reference)	-	1.000 (Reference)	-	1.000 (Reference)	-
Age						
• Elderly	-	-	-	-	-	-
• Adult	0.592 (0.131)	0.495	0.937 (0.293)	0.913	-	-
• Adolescent	-	-	-	-	-	-
Domicile						
• East Java	0.437 (0.585)	0.058	1.921 (0.606)	0.267	1.024 (0.598)	0.929
• Central Java	1.750 (0.594)	0.594	3.111 (0.983)	0.053	0.785 (0.183)	0.745
• West Java	1.000 (Reference)	-	1.000 (Reference)	-	1.000 (Reference)	-
Marital status						
• Married	-	-	0.361 (0.233)	0.193	-	-
• Non-married	-	-	-	-	-	-
Education						
• High	0.857 (0.272)	0.558	0.511 (0.222)	0.108	0.928 (0.568)	0.525
• Low to medium	1.000 (Reference)	-	1.000 (Reference)	-	1.000 (Reference)	-
Occupation						
• Working	1.428 (0.474)	0.522	0.722 (0.319)	0.442	1.291 (0.729)	0.345
• Not Working	1.000 (Reference)	-	1.000 (Reference)	-	-	-
Income						
• High	2.5 (0.920)	-	0.108 (0.110)	0.575	0.761 (0.277)	0.539
• Low to Medium	1.000 (Reference)	-	1.000 (Reference)	-	1.000 (Reference)	-

*Significant at p value < 0.05

DISCUSSION

Sociodemographic factors

The mean age of the sujects of the three groups was similar in the range of 30-33 years old. The age of the sujects did not affect the emergence of somatic symptoms in all subjects. The effect of age in emotional responses to stress remains unclear. Previous studies showed that the age of subjects affect the emotional response to stress. The older subjects were more susceptible to stress compared to younger subjects.[9,10] However, another study reported that younger people (20-44 years old) experienced higher stres9 and depression compared to older people (>44 years old).[12]

In contrast to the age, the sex was significantly correlated with the emergence of somatic symptoms in this study. Females and males were more likely to express different reactions to stress both psychologically and biologically.[13] Furthermmore, it was reported that female were more likely to suffer under depression compared to male.[12,14,15] The

marital status did not affect the somatic symptoms in this study. This was due to 98% of the subjects involved in this study were married. Previous studies reported that married individuals were at higher risk of somatic symptoms compared to those who have not married on the basis of risk ratio (RR).[12,16-18]The education, occupation, and income did not affect the somatic symptoms in this study. Previous studies showed that subjects with higher education level havehigher depression risk.[12] In contrast, another study reported that subjects with lower education levels experienced somatic symptoms 1.36 higher than those with higher education levels.[18]

The domicile also did not affect the somatic symptoms in this study. Domicile represents a place for people to permanently live for a certain period of time. It describes the environment and way of thinking of the people where they live that affect their response to stress. The depression was more likely experienced by people who live in a metropolitan. The more modern of socialcultural of people, they were more susceptible to the emergence of somatic symptoms due to the presence of psychological stress and depression.[14]

The correlation of seropositive IgG level and somatic symptom level

No correlation between the IgG anti-*T. gondii* and anti-CMV and somatic symptoms was observed in this study. The correlation between chronic diseases and somatic symptoms or stress has been investigated previously with different results. Leavens *et al.*[19] reported that there is no different of somatic symptoms among patients with systemic sclerosis comapared to healthy people. In contrast, Glise *et al*.[18] reported that there is correlation between patients with exhaustion disorders and somatic symptoms. In addition, the prevalence of somatic symptoms increased in headache patients or cancer patients.[20,21]

Recent study showed that the sychological factors are associated to individuals' immune system. Stressful conditions could cause inflammation and activation of hypothalamic-pituitary-adrenal (HPA) that induce adreno-cortico-tropic hormone (ACTH) to release stress hormone cortisol.[18] The cortisol could inhibit the circulation of leukocyte cells in the blood from locations of inflammation.[19] In addition, the cortisol hormone could block immunoglobulin or antibody synthesis, which are necessary in humoral immunity response. The cortisol could also trigger lymphocyte network atrophy in the thymus, spleen, and spleen glands.[22-24] In addition to immunological effects, it also could influence human behavior and emotion such as being easily irritated and depressed.[19]

Stress could decrease the number and the function of lymphocyte T cells (CD4+, CD8+) and cytokine IL-2 that cause the lymphocyte T cells more tolerant to infection in inflammation reactions.[23,25]

CONCLUSION

In conclusion, the percentage of the patients with *T. gondii* and CMV infections who suffer somatic symptoms in six big cities in Java is high (54.4%) with the PR vary from 0.954 to 1.333. However, it is not correlated with the *T. gondii* and CMV infections. The different laboratory in the IgG anti-*T. gondii* and anti-CMV examinations may contribute in the variation of results of the IgG examination.

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