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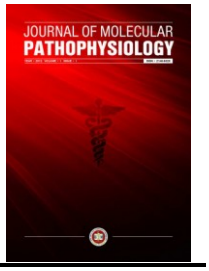

Original Research

Role of intracellular adhesion molecules-1 (ICAM-1) in the pathogenesis of toxoplasmic retinochoroiditis

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Abstract
Background: *T*oxoplasmic retinochoroiditis is the most common cause of posterior uveitis (intraocular inflammatory syndrome) in immunocompetent patients. Leucocytes- endothelial adhesion is an early step in many inflammatory disorders that mediated by endothelial cell adhesion molecules. Intercellular adhesion molecule-1 (ICAM-1) was reported to be upregulated in retinal inflammatory diseases.
Objective: The present study aimed to determine the frequency of *T. gondii* infection among patients presented with retinal inflammatory lesions and also, determine whether the ICAM-1 implicated in the pathogenesis of toxoplasmic retinochoroiditis.
Methods: Forty four patients with retinal inflammatory lesions, 44 healthy controls without any ocular manifestations were subjected to determine anti- *Toxoplasma* IgG antibodies seropositivity and soluble intercellular adhesion molecule-1 (sICAM-1) serum level using the commercially available enzyme linked immunosorbent assay kits.
Results: The results of this study showed that the frequency of anti- *Toxoplasma* IgG antibodies among ocular group (59.1%) was high statistically significant than that in healthy control group (18.2%). Regarding the level of the sICAM-1 in ocular Toxo positive subgroup, there was significantly higher level compared to ocular Toxo negative subgroup and healthy control Toxo positive subgroup. Also, it was significantly higher than healthy control Toxo negative subgroup. Concerning the healthy control group, there was significantly higher level of sICAM-1 in Toxo positive subgroup compared to Toxo negative subgroup.
Conclusion: The findings suggested that ICAM-1 expression might be implicated in the pathogenesis of toxoplasmic retinochoroiditis whereas sICAM-1 could be a good marker reflecting disease severity.

INTRODUCTION

Toxoplasma gondii, an opportunistic parasite, affects the retina and the underlying choroid, causing retinochoroiditis, the most common manifestation of ocular toxoplasmosis [1]. It is responsible for 30 to 50% of posterior uveitis (intraocular inflammatory syndrome) cases in immunocompetent individuals [2]. Toxoplasmic retinochoroiditis may occur either immediately or long after the initial infection or in reactivation [3,4]. Recurrent attacks of toxoplasmic retinochoroiditis might result from rupture of dormant cysts in the retina and release viable parasites that induce necrosis and inflammation or hypersensitivity reaction to parasite antigen [5]. The intensity of damage to retina and choroid depends on the severity of the infection and the associated inflammatory reaction. Within the retina, lysosomal and other autolytic enzymes released by inflammatory cells predominantly macrophages and lymphocytes are thought to contribute to the pathogenic mechanisms of retinal tissue damage [6].

The clinical diagnosis of toxoplasmic retinochoroiditis is based upon ophthalmoscopic examination. The typical fundus abnormalities present as grey-white focus of retinal necrosis with adjacent choroiditis, vasculitis, hemorrhage and vitreitis. Active

inflammation lasts about 6 weeks, at which time the lesion will begin to regress, leaving behind a characteristic macular pigmented scar on the retina [1]. However, atypical lesions also occur, including punctate outer retinitis, neuroretinitis and papillitis and their toxoplasmic origin can be demonstrated only by laboratory testing or by a positive response to specific treatment [7]. The laboratory diagnosis of toxoplasmosis is based on detection of antibodies and *T. gondii* DNA using polymerase chain reaction (PCR) which support clinical findings [8].

Human retinal endothelial cells are more susceptible to infection with *T. gondii* tachyzoites than other subpopulations of endothelial cells [9]. Leucocytes-endothelial adhesion is an early step in many inflammatory disorders; adhesion of leucocytes to endothelial cells is mediated by endothelial cell adhesion molecules which are classified into three groups according to their structure; selectins, integrins and the immunoglobulin supergene families. These molecules are important for the transmigration of leukocytes to the sites of inflammation and for the recognition between leukocytes and arriving target cells [10]. It has shown that several cytokines activation up-regulate dramatically the expression of these cellular adhesion molecules and thus increase the adhesiveness between leukocytes and the endothelium [11]. The role of adhesion molecules in uveitis and other inflammatory diseases of the eye is well documented [12,13]. Immunohistochemistry studies reported constitutive low level expression of intercellular adhesion molecule-1 (ICAM-1), a membrane glycoprotein belonging to the immunoglobulin supergene family, in the normal retina [14,15]. ICAM-1 was reported to be upregulated in retinal inflammatory diseases [16,17]. The secretion of ICAM-1 by retinal pigment epithelium in response to *T. gondii* infection is documented [18]. Soluble intercellular adhesion molecule-1 (sICAM-1) which represents a circulating form of ICAM-1 resulted principally from proteolytic cleavage (shedding) of membrane ICAM-1[19] .It has been suggested that sICAM-1 which is detected in human serum is an early marker of immune activation and response [20,21]. Higher serum levels of sICAM-1 may indicate endothelial dysfunction and reflect more intense inflammation [22]. It was found to be elevated in the vitreous fluids of patients with uveitis and proliferative vitreoretinal disorders [23,24]. Palmer et al [25] and Zaman et al [26] also found a relation between ocular disease activity and sICAM-1 levels. Elevated production of ICAM-1 by *T. gondii*-infected resident cells may initiate local immune reactivity during primary infections and during recurrent reactivation episodes in *Toxoplasma*-induced retinochoroiditis [18].

The present study aimed to determine the frequency of *T. gondii* infection among patients presented with retinal inflammatory lesions and also, determine whether the ICAM-1 implicated in the pathogenesis of toxoplasmic retinochoroiditis.

MATERIAL AND METHODS

Subjects:

The present study was performed on 44 patients (ocular group) who referred to the Parasitology Department, Research Institute of Ophthalmology, Giza- Egypt from January 2009 to January 2010. The patients presented with retinal inflammatory lesions that could be caused by toxoplasmosis; their clinical findings of retinitis, retinochoroiditis vitreitis, macular scar, chorioretinal scar or optic atrophy. Also, 44 subjects without any ocular manifestations were included in this study as healthy control group which were chosen from the health-care workers and the relatives of the patients. The study was approved by Research Ethics Committee, Faculty of Medicine, Ain Shams University, and informed consent was obtained from all participants.

Five milliliters of blood were taken under sterile conditions from all participates. The sera were separated and stored at -20ºC until the analysis for anti-*Toxoplasma* IgG antibodies and determination of the sICAM-1 serum level.

Detection of anti- *Toxoplasma* IgG antibodies:

All serum samples were tested for IgG anti-*T. gondii* antibodies using commercially available enzyme linked immunosorbent assay (ELISA) kit (DRG International, Inc., USA). All reagents and controls were supplied by the manufacturer. Serum samples, negative control, positive control and calibrators were diluted at 1:40 dilution. Then, 100 µl of diluted sera, controls and calibrators were dispensed into the appropriated wells of microtiter plate coated with purified *T.gondii* antigen and incubated at 37ºC for 30 min. Horseradish peroxidase-conjugated antibody (100 µL) was then added to react with the bound antibody. Substrate (100 µL) for peroxidase was added and the reaction was stopped by stop solution (100 µL). The optical densities were read at 450 nm in an ELISA reader. The mean of duplicated cut-off calibrator value (32 Iµ/ml), positive control, negative control and serum samples were calculated. Toxo G index of each determination were calculated by dividing the mean values of each sample by calibrator mean value. A sample was considered positive for IgG when a Toxo G index was equal or greater than 1.0 (>32 Iµ/ml), a negative reaction corresponds to Toxo G index less than 0.90 (<32

Iμ/ml), and an equivocal result to Toxo G Index between 0.91-0.99.

According to the results of ELISA test, each group enrolled in this study was divided into two subgroups as follow: ocular Toxo positive (IgG +ve), ocular Toxo negative (IgG -ve), healthy control Toxo positive, healthy control Toxo negative.

Determination of the sICAM-1 serum level:

Serum levels of sICAM-1 were detected using a commercially available enzyme-linked immunosorbent assay (ELISA, Quantikine Human sICAM-1/CD54 Immunoassay R&D Systems, Inc., USA) according to the manufacturer's instructions. This assay employs the quantitative sandwich enzyme immunoassay technique. Serum samples were diluted in calibrator diluents at 1:20 dilution. 100 μl of standards, samples, controls, and conjugate are pipetted into the appropriated wells of microtiter plate coated with monoclonal antibody specific for sICAM-1, incubated for 1.5 hours at room temperature and any sICAM-1 present is sandwiched by the immobilized antibody and the enzyme-linked monoclonal antibody specific for sICAM-1. Following a wash to remove any unbound substances, 200 μl of substrate solution were added to each well and incubated for 30 minutes at room temperature with protection from light and the reaction was terminated by a stop solution (50 μL). The final adsorbance was determined at 450 nm using a microplate reader. Values of samples were calculated from a standard curve generated from standards of known concentration.

Statistical analysis:

Collected data were coded, tabulated and introduced to a PC using the Statistical Package for Social Science (SPSS) for windows version 11.0. The chi-square ($\chi 2$) was used to analyze the frequency of anti- *Toxoplasma* IgG antibodies in the study groups. The level of sICAM-1 in the studied subgroups was expressed as mean ±SD. These means were compared between subgroups using Student's *t*-test to clarify statistically significant differences. $P<0.05$ was considered statistically significant (sig.) and $P<0.0001$ was considered statistically highly significant.

RESULTS

In the present study, 26 out of 44 (59.1%) patients of ocular group and 8 out of 44 (18.2%) of healthy control group were positive for anti- *Toxoplasma* IgG antibodies, this difference was highly statistically significant ($P<0.0001$) (Table 1).

Table 1. Frequency of *T. gondii* infection among the studied groups.

Studied groups	No. 88	anti- *Toxoplasma* IgG		$\chi 2$	*P-value
		IgG +ve No. (%)	IgG-ve No. (%)		
Ocular group	44	26(59.1%)	18(40.9%)	15.529	P<0.0001 Highly sig.
Healthy control group	44	8 (18.2%)	36(81.2%)		

*Ocular group versus (vs) healthy control group.

Table 2. sICAM-1(ng/ml) concentration among the different studied subgroups.

Studied groups		No	Mean ±SD	Range (ng/ml)	Median (ng/ml)	*P*-value
Ocular group	**Toxo positive**	26	255.1±173.8	110-1000	207	*P*1 < 0.05 sig *P*2 < 0. 05 sig *P*3 <0.0001 Highly sig
	Toxo negative	18	153.7±55.6	54-252	150	-
Healthy control group	**Toxo positive**	8	183.3 ±63.3	102.4-290	174.5	*P*4<0.0001 Highly sig
	Toxo negative	36	72.9±49.1	10-162	54	

*P*1 = Toxo positive vs Toxo negative in ocular group.
*P*2= Toxo positive in ocular group vs Toxo positive in healthy controls.
*P*3= Toxo positive in ocular group vs Toxo negative in healthy controls.
*P*4= Toxo positive in healthy controls vs Toxo negative in healthy controls.

DISCUSSION

Toxoplasmic retinochoroiditis is partly due to the lysis of the retinal cells infected with the parasite and partly to the adjacent inflammatory response in the choroid and retina [27]. Inflammation associated with retinochoroiditis is a major complication of ocular toxoplasmosis in infants and immunocompetent individuals. Moreover, *T. gondii*-induced retinal disease causes serious complications in patients with AIDS and transplant patients. During natural infections, *Toxoplasma* initially crosses the intestinal epithelium, disseminates into the deep tissues and traverses biological barriers as the blood–retina barrier [28]. Within this immunologically privileged site, it causes severe ocular pathology in immunocompetent individuals [29]. The factors that contribute to the pathogenesis of toxoplasmic retinochoroiditis include the ability of the parasite to infect cells of the eye and to persist at this site in dormant cysts. Recurrences of ocular lesions usually develop at the border of old scars and are attributed to rupture of tissue cysts located within the old lesions. The rupture may be triggered either by changes in the parasite metabolism or by the host immune response. These can then give rise to tachyzoites that rapidly infect adjacent cell, multiply, proliferate in specialized parasitophorous vacuoles and destroy ocular tissues [30]. In the severe form of *T. gondii*-induced uveitis, destruction of large segment of the outer retina and pigment epithelium is observed [31]. Retinal pigment epithelium (RPE), an integral part of the neuroretina in the posterior pole of the eye, acts as a barrier between the highly vascularized choroid and the retina with a complex architecture of neuronal cells. Because of its critical location and physiological activities, is constantly subjected to contact with various infectious agents including *T. gondii* [32]. Histopathological examination of the relevant tissues of the eyes from patients with *Toxoplasma*-induced retinochoroiditis revealed the presence of free tachyzoites and cysts in the RPE and the inner layers of the neurosensory retina [31].

ICAM-1 is a widely distributed molecule, and its expression is highly regulated. Normally, the basal ICAM-1 expression is low on nonhematopoietic cells such as normal RPE cells, but it can be up-regulated by a variety of cytokines, including interleukin 1(IL-1β), tumor necrosis factor (TNF-α), and interferon-gamma (IFN-γ) which might be partially present in pathologically altered intraocular environments [33]. In response to the infection with *T. gondii*, the host organism sets up an immune reaction mainly of cellular type, via T lymphocytes – essentially helper T lymphocytes (Th1) with prominent production of IFN-γ, TNF-α and IL-1β that have a protective role on the reduction of the toxoplasmic retinochoroiditis [27,30,34]. It has been shown that IFN-γ stimulates expression of ICAM-1 in human RPE cells [35]. Portillo et al [17] showed that endothelial cells, Müller cells, microglia/ macrophages, astrocytes, ganglion cells, and photoreceptors also, expressed ICAM-1. *T. gondii* exploits ICAM-1 that expressed on endothelial cells for enhanced its invasion into deep tissues [36]. ICAM-1 secretion by RPE cells might actively participate in immune reactions in the retina by recruiting and activating lymphocytes, contributing to the immunopathologic process in inflammatory diseases. From this point of view, the present study determined the frequency of *T. gondii* infection among patients presented with retinal inflammatory lesions that could be caused by toxoplasmosis and also, determine whether the ICAM-1 implicated in the pathogenesis of toxoplasmic retinochoroiditis in those patients.

Results obtained in the present study showed that the clinical diagnosis of ocular toxoplasmosis may be supported by laboratory tests in 59.1% of cases in agreement with other reports which detected prevalence ranged from 2% in the United States [37] to 99.5% in southern Brazil [38]. The diversity in seropositivity rates regarding the previous studies and our study might be attributed to the timing of infection either congenital infection, with recurrences many years later, or postnatally acquired infection, with ocular disease at the time of infection, risk factors for ocular involvement especially in immunocompromised patients [39], host immune function, host genetic factors as the development of large numbers of cysts is controlled by the major histocompatibility class I L^d gene [40], and variations in virulence of *T. gondii* isolates. Such differences in virulence may be associated with difference in incidence or clinical manifestations of ocular disease [29]. On the other hand, the frequency of *T .gondii* infection in the healthy control group (18.2%) enrolled in this study was comparable with that detected in other healthy population, 20.3% by Sunder et al [41] and 17.2% by Joshi et al [42]. This asymptomatic infection may be due to effectiveness of the immune system. Asymptomatic immunocompetent individuals might represent a risk group supporting the idea of recurrent disease, as reported previously [43]. The presence of circulating parasites in blood of those immunocompetent individuals may be associated with the reactivation of the ocular disease.

Regarding the higher levels of the sICAM-1 in ocular Toxo positive subgroup enrolled in this study, this up-regulation of sICAM-1 expression is believed to be a specific response to the interaction between host cells and the parasite at different stages of parasite infiltration, parasite intracellular replication, and/or release of parasite secretion and degradation products

[18]. In those Toxo positive cases, serum levels of ICAM-1 varies from one case to another and seems to be correlated with the severity of pathological changes. Moreover, the higher levels of sICAM-1 in those ocular Toxo positive subgroup reflected more intense inflammation associated with toxoplasmic retinochoroiditis as ocular toxoplasmosis typically manifests itself through exacerbations of chorioretinitis resulting from the rupture of quiescent cysts in the retina that release the bradyzoites, a form of the parasite with low levels of metabolic activity, which transform into tachyzoites, the form of the parasite with high levels of metabolic activity, and reactivate infection locally [27]. In accordance with the results of this study, Zaman et al [26] demonstrated that raised levels of sICAM-1 are readily detectable in the sera of patients with posterior uveitis, and have shown that raised sICAM-1 levels are significantly associated with disease relapse. Increased expression of ICAM-1 on the retinal pigment epithelial cells of uveitis patients [44] and on epiretinal membranes that formed in chronic uveitis [33] has also been reported. It was found that ICAM-1 has been detected in histological sections of the eyes with uveitis [45]. Of relevance, ICAM-1 has been detected in vitro in cultured glia and neurons as well as in vivo in the external limiting membrane of the retina and photoreceptor aggregates in patients with macular degeneration [15,46]. Furthermore, Nageneni et al [18] concluded that the secretion of ICAM-1 by RPE cells may play a critical immunoregulatory role in the pathophysiological processes associated with *T. gondii*-induced retinochoroiditis. These observations together with our obtained results indicated that the high level of ICAM-1 expression might be involved in the pathogenesis of toxoplasmic retinochoroiditis.

The current study reported low sICAM-1 levels in healthy controls Toxo positive subgroup (asymptomatic toxoplasmosis) that had no signs suggesting acute infection. This could be explained by the predominance of a minimal inflammatory response and cell damage at this stage of infection due to latency of the disease resulting from the existing balance between the host immune response and the parasite [47]. The gradual elevation of the anti-inflammatory Th2 response reported during the chronic stage of toxoplamosis [34] could give another explanation for the reported low sICAM-1 levels. This Th2 response has an expected inhibitory effect on the secretion of Th1 cytokines that up-regulate the expression of ICAM-1 [48].

In conclusion, the findings of the present study suggested that ICAM-1 expression might be implicated in the pathogenesis of toxoplasmic retinochoroiditis whereas sICAM-1 could be a good marker reflecting disease severity. It is recommended the use of immunomodulatory therapies not only be directly towards this cellular adhesion molecule but might indirectly disturb its expression by influencing the stability of the blood-retina barrier or by interfering with cytokine action to modulate toxoplasmic retinochoroiditis immunopathogenesis.

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