**Abstract**

Introduction: *Toxoplasma gondii*, a common parasitic infection, has a special affinity to the brain. It has a lifelong existence without an apparent clinical disease. While the etiology of bipolar disorder (BD) remains unclear, epidemiological studies suggest a role for infections. Central nervous system is particularly susceptible to oxidative stress (OS) because of its high metabolic rate and its low levels of antioxidant defenses. OS is a contributor to the initiation and progression of many neurological illnesses. OS injury is a constantly and compelling finding associated with BD and toxoplasmosis. Aim: This cross-sectional study has investigated a possible role of toxoplasma-induced OS in the development of BD. Methods: Healthy controls and BD patients were examined for anti-*Toxoplasma* immunoglobulin-G (IgG) and two protein (3-nitrotyrosine) and DNA (8-hydroxy-2’ deoxyguanosine [8-OHdG]) OS markers. Results: *Toxoplasma* positivity was higher (40%) among BD patients compared to controls (12%). Significantly higher levels of anti-*Toxoplasma* IgG were detected in BD patients compared to controls. Nitrotyrosine (796.7 ± 106.28) and especially 8-OHdG (20.31 ± 8.38) were significantly higher among toxo-positive BD compared to toxo-negative BD (675.97 ± 144.19 and 7.44 ± 2.86) and healthy controls (464.02 ± 134.6 and 4.17 ± 1.43). Conclusion: These findings might indicate a role for *Toxoplasma* infection in the development of BD, possibly through creating a highly oxidative brain environment.

Keywords: 3-nitrotyrosine, 8-hydroxy-2’-deoxyguanosine, bipolar disorder, oxidative stress, *Toxoplasma*

**INTRODUCTION**

Bipolar disorder (BD) is a chronic mood disorder and a main cause of disability among young patients. Individuals with BD experience disruptive episodes of mania or hypomania and depression. It has a worldwide prevalence of approximately 1%–2% among adults and leads to cognitive and functional impairment. The course of BD often has remissions, but recurrence usually happens.

*Toxoplasma gondii* is a zoonotic intracellular protozoan parasite that infects over 30% of the human population. The parasite has a special predilection to the brain and survives mainly in neuronal tissue for a unique lifelong chronic phase of the disease.

Like other psychiatric disorders, there is no diagnostic laboratory biomarker for BD. Diagnosis is solely made on clinical basis and directed interview with the patient and his/her relatives. Integration of clinical data with laboratory biomarkers and neuro-imaging findings is crucial to properly diagnose and monitor this disorder.

Very little is known about the specific biological mechanisms underlying BD; however, research concerning the pathophysiology of BD has gained momentum over the past few decades. Although this disorder exhibits a strong evidence of genetic influence, a multifactorial hypothesis is thought to better explain BD etiology where an interaction...
between environmental factors and genetic background is suggested.[9] Better understanding of the pathophysiological processes underlying BD, hopefully, might lead to objective biomarkers that could aid prognostic accuracy as well as early diagnosis.[9]

Many studies have demonstrated a correlation between T. gondii seropositivity and personality changes,[9,10] as well as various psychiatric disorders including schizophrenia[11] and depression.[12] Such a relationship has also been reported for other neuropsychiatric diseases such as epilepsy, Alzheimer’s disease, and Parkinson’s disease.[9,13] However, the pathophysiologic mechanisms underlying such changes are still not fully understood.[14]

Reactive oxygen species (ROS) are constantly generated in cells as part of the physiological and metabolic processes. Under physiological conditions, a balance, involving reactive oxidants and various antioxidant defenses, is sustained.[15] Due to their reactive nature, these endogenously produced ROS induce changes to cell membrane lipids, nucleic acids, and proteins, particularly in mitochondria, impairing mitochondrial energy production.[16] Impaired energy and high ROS combined or individually can cause cell dysfunction and result in cell death, either by necrosis or by apoptosis. Symptoms of organ dysfunction appear once enough cells became either dysfunctional or dead.[17] Damage to macromolecules, membrane lipid-polysaturated fatty acids, DNA/RNA as well as proteins was reported to occur in BD by ROS and nitrogen species.[18-20] This oxidative overexpression could explain the hastened aging, premature mortality, and cognitive impairment encountered in BD.[21]

Toxoplasma-mediated oxidative stress (OS) is suggested to take part in the mechanism of neuropahtology and neurodegeneration.[22] A pro-inflammatory immune reaction, dominated by Th1 and Th17 cytokines, particularly interferon (IFN-γ) and TNF-α, is triggered by Toxoplasma infection.[23] IFN-γ is the main and crucial cytokine for defense against T. gondii, particularly in central nervous system (CNS). However, a pathological arm of this defense mechanism does exist. IFN-γ-activated microglia produce toxic reactants, mainly nitric oxide (NO), that induce brain tissue injury and neuronal inflammatory pathologies. Toxoplasma-induced IFN-γ also triggers high levels of NO as a mechanism for arginine degradation.[24]

8-hydroxy-2-deoxyguanosine is a dominant form of free oxidative lesions of nuclear and mitochondrial DNA. It is a critical biomarker for measuring the effect of endogenous oxidative DNA damage and as a risk factor for many diseases including cancer.[25] Nitrotyrosine is generated through nitration of tyrosine residues in different proteins. This oxidative modifications of proteins can affect some of their functions such as enzymatic activity, DNA binding, and susceptibility to degradation.[26] 3-nitrotyrosine (3-NT) has been utilized as a pivotal biomarker for in vivo oxidative insult caused by ONOO−.[27] In the current study, both markers (8-hydroxy-2’-deoxyguanosine [8-OHdG] and 3-NT) were used to assess a possible role for Toxoplasma-induced OS in the pathogenesis of BD.

It is unlikely that a sole mechanism, utilized by T. gondii during infection, would justify all neuropsychiatric changes induced by toxoplasmosis and known to exist in BD. However, we suggest that oxidative and nitrosative stress, induced by Toxoplasma infection, has a major role in the development of BD, either directly or through mediating other pathways. If this suggestion stands, markers of OS those dominate, but at different levels, throughout the different phases of Toxoplasma infection could be utilized as diagnostic and/or prognostic indicators of BD. This study was conducted to investigate a possible role for Toxoplasma-induced OS in the development of BD.

Materials and Methods

Subjects

The study participants (n = 40) were recruited from inpatient wards and outpatient clinics of psychiatric departments of some general hospitals and psychiatric diseases/mental health hospitals in Makkah Region, Saudi Arabia. Patients were diagnosed as having BD according to the Diagnostic and Statistical Manual of Mental Disorders.[28] Patients had no other substantial medical conditions or taking medications other than those related to BD. Some rejection criteria were applied, mainly the absence of the complete data set of the patient as designed in the psychological evaluation report and the presence of current or past history of substance abuse or mental deficiencies or neurological disorders that could have an influence on cognitive performance such as epilepsy, mental retardation, head trauma, or history of encephalitis. Demographically matched healthy volunteers (n = 25) were selected from the same communities of the participating BD patients. For a volunteer to be included in the control group, she/ she should be an apparently healthy person with no documented or suggestive present, past, or family history of psychiatric disorders and without current or past history of substance abuse. Controls were nonsmokers and were not taking medication. All participants were informed orally and in writing. All participants gave written informed consent.

The BD group (forty patients) was subdivided, according to anti-Toxoplasma immunoglobulin-G (IgG) positivity, into two subgroups: Toxoplasma-positive BD group (16 patients) and Toxoplasma-negative BD group (24 patients).

Samples and assays

Sera extracted from the blood samples (3–5 ml) collected from all patients and controls, after a written informed consent, were subjected to analyses for anti-Toxoplasma IgG, 3-NT, and 8-OHdG.

Immunoglobulin-G enzyme-linked immunosorbent assay

Sera of all participants (patients and controls) were analyzed for Immunoglobulin-G enzyme-linked immunosorbent assay (ELISA)
kit (“Toxoplasma IgG” NovaTec Immundiagnostics GmbH, Dietzenbach, Germany). The procedure was done following the manufacturer’s instructions. Absorbance values of all control and test samples were converted to IgG concentration units (IU/ml) according to an absorbance versus concentration (standard calibration) curve. Positivity was considered for values >35 IU/ml.

**Human 3-nitrotyrosine and 8-hydroxy-2’-deoxyguanosine by enzyme-linked immunosorbent assay**

To assess protein oxidation, levels of 3-NT were determined, in sera of the study participants (patients and controls), with a commercially available ELISA kit (Uscan Life Science Inc., Wuhan, USA), for human nitrotyrosine, following the manufacturer’s instructions. Participants’ serum concentrations of 3-NT were expressed as pg/ml. Serum values of 8-OHdG were determined, as a biomarker for DNA oxidation products, using a commercially available 8-OHdG ELISA kit” (JaICA, NIKKEN SEIL co., Japan) conforming to the manufacturer’s instructions. Serum concentrations of 8-OHdG for all participants were expressed in ng/ml.

**Statistical analysis**

The analyses for this study were performed using IBM SPSS Statistics for Windows, Version 23.0. (Armonk, NY: IBM Corp., USA). Descriptive analyses for demographic characteristics and laboratory values were expressed as means and standard deviations. Demographic and clinical characteristics were assessed using Chi-square test and one-way analysis of variance, with a significance level of $P < 0.05$. As laboratory results (anti-toxo IgG, 3-NT, and 8-OHdG) showed a nonparametric distribution, among different groups, they were analyzed using Student’s $t$-test and Kruskal–Wallis test as indicated.

**Results**

The participants’ characteristics, related to age and sex, are summarized in Table 1. A slightly greater, yet insignificant, prevalence of female over male patients was found in BD patients, especially those who are Toxoplasma positive. There was no significant difference on the mean age of the different groups.

The prevalence of significant anti-Toxoplasma IgG, indicative of Toxoplasma positivity, was higher (40%) among BD patients compared to controls (12%). Numerical values of IgG were significantly higher ($P < 0.001$) in patients with BD compared to normal controls [Table 1 and Figure 1].

Protein oxidative nitrosylation, as measured by 3-NT, was increased significantly [Table 1] in the bipolar group compared with controls, especially in Toxoplasma-positive patients. While 3-NT levels were still significantly higher ($P < 0.01$) in toxo-positive BD patients compared to toxo-negative ones [Figure 2], however, it was not as striking as in the case of 8-OHdG ($P < 0.005$) [Figure 3].

Levels of 8-OHdG, as a measure for DNA oxidation, were significantly higher [Table 1] in patients with BD, especially those positive for toxoplasmosis ($P < 0.01$ and $P < 0.0001$, respectively) compared to controls. We observed also an almost 3-fold increase in the levels of 8-OHdG in BD cases that are toxo positive compared to toxo negative ones ($P < 0.005$) [Figure 3].

**Discussion**

As far as we know, this study is the first to explore, not only the association between Toxoplasma infection and BD, but also to establish a causal link for the parasite in the pathogenesis of such illness.

In contrast to other psychiatric disorders, like schizophrenia, the relationship between Toxoplasma infection and BD is less recorded and more ambiguous. While some studies[29-31] positively correlate toxoplasmosis and BD, a considerable number of reports[32,33] deny such relationship.

There is a considerable overlap between neurobiological and biochemical characteristics of BD and the changes inflicted by Toxoplasma infection in the local brain environment. Toxoplasma infection might represent a main environmental

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**Table 1: Demographic and laboratory parameters in the different study groups**

|                      | Controls (n=25) | BD (n=40) | Toxoplasma-negative BD (n=24) | Toxoplasma-positive BD (n=16) | $P$   |
|----------------------|----------------|-----------|------------------------------|-------------------------------|-------|
| **Gender (%)**       |                |           |                              |                               |       |
| Male                 | 14 (56)        | 19 (47.5) | 12 (50)                      | 7 (43.75)                     | 0.65* |
| Age (years)          | 24.4±4.6       | 32.6±8.2  | 26.8±9.4                     | 41.3±7.2                      | 0.72**|
| Anti-toxoplasma IgG (IU/ml) | 7.95±3.76     | 85.96±74.96 | 12.95±3.28                  | 195.49±86.77                  |       |
| NT (pg/ml)           | 464.02±134.6   | 724.26±143.2 | 675.97±144.19               | 796.7±106.28                  |       |
| 8-OHdG levels (ng/ml)| 4.17±1.43      | 12.21±8.79 | 7.44±2.86                    | 20.31±8.38                    |       |

*Chi-square test, **Student’s t-test. BD: Bipolar disorder, IgG: Immunoglobulin-G, NT: Nitrotyrosine, 8-OHdG: 8-hydroxy-2’-deoxyguanosine
Several studies have indicated a crucial share of lipid, protein, and DNA peroxidation in the pathophysiology of BD. Therefore, the current study investigated the role of protein and DNA peroxidation biomarkers in patients with BD, especially those infected with *T. gondii*.

The results of this study showed that *Toxoplasma* infection has a significant link to BD which could be through the OS induced by the parasite, which was also demonstrated in our results. This interesting triology of interplaying *T. gondii*, OS, and BD, revealed in this study, could be explained on the basis of mitochondrial dysfunction, which is one of the most accepted hypotheses for the development of BD. Dysfunctional mitochondria produce ATP less efficiently, but more competent in producing ROS. Oxidative overexpression and apoptosis due to mitochondrial dysfunction play a role in the pathophysiology of common neurodegenerative disorders such as Parkinsonism and Alzheimer’s disease. Recently, a mitochondrial dysfunction-based model has been hypothesized to interpret the phenomenal biphasic energy dysregulation in BD mania and depression phases. A significant decline in the activity of antioxidant defense system has been demonstrated in *Toxoplasma*-seropositive patients.

Some studies have shown that inhibitors of mitochondrial function and inducers of OS can induce *Toxoplasma* encystment in *vitro*. This study demonstrated a high percentage of BD cases that are seronegative for toxoplasmosis. This does not invalidate the hypothesis of the study, as it was not expected that *T. gondii* will be the sole infectious agent responsible for all BD cases. We believe that infectious agents, other than Toxoplasma, could precipitate BD if they have the same brain predilection, and can trigger the same OS pathways. Cytomegalovirus (CMV), for example, shares some of the *Toxoplasma* infectious patterns that could make it a possible candidate to trigger BD. CMV is a common infection and even more common than *T. gondii*; has a lifelong existence within the host, with a special affinity to nervous tissues; and its congenital infection might lead to severe CNS consequences. Similarly, most immunocompetent individuals who acquire CMV as children or adults show no signs of illness or have mild symptoms, while immunocompromised ones will experience the most severe forms of nervous system involvement. Sero-negative pregnant women are at a high risk of *in utero* transmission of CMV infection if primarily infected with the virus during pregnancy, a phenomenon that is well documented in toxoplasmosis. Latent infection with CMV was reported to have a significant association with overexpressed OS. Weis et al. reported an upregulated OS caused by CMV in endothelial cells, playing a part in transplant arteriosclerosis. Therefore, *Toxoplasma*-negative BD patients could be latently infected with other infectious agents that have similar criteria of pathogenesis as *T. gondii*, an assumption that was not investigated in the current study.

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One of the limitations of the current study is that individual groups have a small sample size, restricting the adjustment for confounding variables other than age, gender, and *Toxoplasma* infection creates a host’s immunological environment with escalating OS marked by overproduction of toxic free radicals such as ROS and NO.
infection. This consequently hindered the use of such markers for staging BD. The cross-sectional design of the study disabled us from concluding meaningful information about the course of the illness. While the results of the current study should be deduced within the context of such limitations, they create the basis for new prospective large-scale studies in the same direction.

**Conclusion**

These results provide an evidence for the involvement of oxidative DNA and proteins damage in BD. They also indicate a role for *Toxoplasma*-induced OS in triggering such illness. We speculate that other infectious agents that have the same predilection to brain tissue like *T. gondii* and could utilize its OS-triggering pathways, could have a role in the development of BD. These findings, if further consolidated by large-scale longitudinal studies, will validate OS biomarkers as reliable diagnostic and/or prognostic indicators that have significant clinical utility.

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**Conflicts of interest**

There are no conflicts of interest.

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