Serological evidences link toxoplasmosis with schizophrenia and major depression disorder

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1. Introduction

Schizophrenia is a common neuropsychiatric disease of unsure etiology affecting 1% of the world’s population. Most of them experience a lifetime disability and about 10% will eventually commit suicide [1]. It overtly manifests in adolescence and early adulthood, but impairments in neuro-integrative function could be encountered earlier [2]. Depression is the most common psychiatric disorder in man with approximately 4% of men and 8% of women are affected [3]. It presents with depressed mood for at least 2 weeks, along with other symptoms that could include sleep and appetite disturbances, decreased energy, suicidal ideation and intention or plan [4].

Little is known about the etiology of schizophrenia and MDD, but a role of early environmental insults during crucial stages of neurodevelopment, has been suggested. The neurodevelopmental hypothesis of schizophrenia has been one of the most acceptable theoretical description of its etiology [5]. Pre- and perinatal infections are largely considered as risk factors for occurrence of psychiatric disorders [6,7]. Animal studies demonstrate that perinatal infections
can result in an offspring with neurological and behavioral malfunction similar to those of schizophrenia [8,9]. Human studies have offered undeniable evidence that the risk of schizophrenia is increased by early-life environmental insults, including prenatal infection, and/or immune stimulation [10]. A proof for an inflammatory background of depression has been demonstrated, where T-cells, monocytes, proinflammatory cytokines, oxidative and nitrosative stress are key pathophysiological factors [11]. Among many pathogens linked to psychiatric disorders [12,13], most of the attention is centered on *Toxoplasma gondii*, a neurotropic parasite that has a life-long latent phase after a usually short and asymptomatic acute stage in immunocompetent individuals [14]. The parasite is never cleared from the nervous system where cell-mediated immune response mediates its long-life existence [15]. This obligatory intracellular parasite affects one-third of the world’s population [16], and produces a wide range of clinical syndromes with an exceptional severity in immunocompromised patients [17]. Early trans-placental infection might result in a fetal multi-system affection that includes serious CNS abnormalities [18].

The conventional view, that latent toxoplasmosis is usually asymptomatic and has no long-term sequelae, has been questioned [19]. There is a compelling evidence that *Toxoplasma* infection manipulates behavior of many intermediate hosts [20]. Infection with *T. gondii* altered behavior of animal models [21] and manipulated the patterns of many neurotransmitters that mediate the development of schizophrenia [22]. Recently, a growing number of investigators have linked *T. gondii* infection to the emergence of schizophrenia [23–27], however, scarce reports have been reported about the relation of MDD and toxoplasmosis [28,29].

Given the known affinity of *T. gondii* to neural tissues and its ability to congenitally induce brain dysfunction, investigating a potential link between *Toxoplasma* infection and the pathogenesis of psychiatric disorders, is a logic approach. Establishing this link might lead to novel preventive and therapeutic arrays. The aim of the current study was to explore a possible role of *Toxoplasma* infection in the development of two common psychiatric diseases, schizophrenia and MDD. Other factors, genetic and environmental, that might influence this association were cautiously explored through demonstration of the role of age, gender and relevant family history.

2. Materials and methods

2.1. Study population

A cross-sectional survey was designed to investigate correlates of psychiatric disorders in the Mecca Region, Saudi Arabia. A probability sample of 280 individuals (aged ≥ 15 years), all fulfilling the diagnostic criteria “The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)” [30], were selected from psychiatric outpatient clinics. All individuals were living within the main three cities, Jeddah, Mecca and Taif, of Mecca Region. A considerable number (178) of patients were excluded because they did not meet the inclusion paradigms for the study. The rejection criteria were: (1) absence of the complete data set of the patient in a designed Psychological Evaluation Report, (2) presence of current or past history of substance abuse, (3) presence of mental deficiencies or a significant neurological disease that would influence cognitive functions including mental retardation, epilepsy, a previous record of head trauma and/or encephalitis. A total of 55 healthy volunteers were selected as apparently healthy individuals of the same age and gender with no history of substance abuse and without documented or suggestive personal or family history of psychiatric disorders. All participants provided written, informed consent.

2.2. Participants sub-grouping

2.2.1. Measures

Participants were categorized in the following manner: (1) seropositivity: participants were dichotomized, according to anti-*Toxoplasma* IgG values, as seronegative where IgG level is <35 International Units (IU)/ml and as seropositive for those with IgG values ≥ 35 IU/ml; (2) serointensity: IgG titer levels were log-transformed to reduce positive skewness, for use as a continuous variable; (3) disease category: participants were identified as either schizophrenic (*n* = 63) or having major depressive disease (MDD) (*n* = 39) according to clinical examination and data retrieved from a psychological evaluation report designed to include DSM-5 criteria.

2.2.2. Covariates

The patient study group (*n* = 102) was subdivided into several subgroups according to different covariates; age in years was self-reported and was categorized as (1) 15–25 (*n* = 18), (2) 26–35 (*n* = 44), or (3) greater than 35 (*n* = 40). Gender was dichotomized as female (*n* = 29) and male (*n* = 73) and relevant family history was dichotomized as positive (*n* = 28) and negative (*n* = 74).

2.3. Laboratory analyses

Blood samples (3–5 ml volume) were collected from all patients and control subjects after a written informed consent. Sera were separated then delivered on dry ice, in a real time manner, to our laboratory where samples were subjected to further processing.

Sera of all participants were analyzed for specific antitoxoplasma IgG and IgM using commercially available ELISA kits (NovaTec Immunodiagnostics GmbH, Dietzenbach, Germany), following the manufacturer’s instructions. Absorbance was read on ELISA microwell plate reader (Awareness Technology Inc., model 3200, USA) equipped for the measurement of absorbance at 450 nm/620 nm. Absorbance values were converted to IgG concentration (IU/ml) according to a standard calibration curve. IgG levels ≥ 35 IU/ml were considered positive. Absorbance values of the IgM assay were expressed as Nova Tec Units (NTU) by calculation following the formula, absorbance value × 10/cut-off. IgM levels ≥ 11 NTU/ml were considered positive.
2.4. Statistical analysis

Statistical testing were performed with SPSS statistical program: version 15.0. Two-sided t- and chi-square tests were used to examine bivariate associations between *T. gondii* category, psychiatric disorders, and covariates of interest. Covariates were considered confounders associated with *T. gondii* infection and predictive of the outcomes of interest. Several comparisons were made between the different test groups in relation to clinical diagnosis, age, gender and relevant family history. P-value < 0.05 was regarded as significant. All test and control values and relations were illustrated in descriptive tables.

3. Results

The prevalence of latent toxoplasmosis (as revealed by anti-*Toxoplasma* IgG positivity) was higher among schizophrenic patients (31.75%) followed by patients with MDD (25.64%) compared to an incidence of 14.55% only in healthy controls. A marked elevation of specific anti-*Toxoplasma* IgG antibody levels, among toxoplasma-positive cases in psychiatric groups (schizophrenia and depression), was observed. These elevated levels were significantly higher compared to the corresponding IgG values in the control group (Table 1).

Toxoplasma positivity rate was lowest in the youngest age group (14–25 years) representing 12.5% only of the schizophrenia group and has no share in the toxoplasma-positive MDD cases. The mean IgG values of schizophrenic as well as MDD patients of this group, were statistically insignificant when compared to control.

Concerning schizophrenic patients, toxoplasma-positivity rate was proportional to age reaching 24% and 43.33% in the middle (26–35 years) and oldest (36–50 years) groups respectively. *Toxoplasma* positivity rate was highest (40%) among the oldest group of MDD patients followed by the middle-aged one (31.58%). Mean IgG values were significantly higher in middle and oldest age groups, among both schizophrenic and MDD patients, compared to their correspondents in the control group (Table 2).

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### Table 1

| Paired groups | Toxo positivity (No/%) | IgG level (IU/ml) (Avg ± SD) | P-value |
|---------------|------------------------|-------------------------------|---------|
| Schizophrenia (n = 63) and Control (n = 55) | 20 (31.57) | 230.1 ± 22.9 | 0.001 |
| MDD (n = 39) and Control (n = 55) | 8 (14.55) | 9.98 ± 1.78 | 0.001 |
| Schizophrenia (n = 63) and MDD (n = 39) | 20 (31.57) | 230.1 ± 22.9 | 0.234 |

* Significant difference if P < 0.05.

### Table 2

| Paired groups | Toxo positivity (No/%) | IgG level (IU/ml) (Avg ± SD) | P-value |
|---------------|------------------------|-------------------------------|---------|
| Schizophrenia (14–25 years) (n = 8) and Control (n = 55) | 1 (12.5) | 28 ± 14.64 | 0.063 |
| MDD (14–25 years) (n = 10) and Control (n = 55) | 8 (14.55) | 9.98 ± 1.78 | 0.156 |
| Schizophrenia (14–25 years) (n = 8) and MDD (14–25 years) (n = 10) | 8 (14.55) | 9.98 ± 1.78 | 0.059 |
| Schizophrenia (26–35 years) (n = 25) and Control (n = 55) | 0 (0.00) | 7.81 ± 5.85 | 0.001 |
| MDD (26–35 years) (n = 19) and Control (n = 55) | 8 (14.55) | 9.98 ± 1.78 | 0.001 |
| Schizophrenia (26–35 years) (n = 25) and MDD (26–35 years) (n = 19) | 6 (24) | 73.8 ± 19.62 | 0.416 |
| Schizophrenia (36–50 years) (n = 30) and Control (n = 55) | 8 (14.55) | 9.98 ± 1.78 | 0.001 |
| MDD (36–50 years) (n = 10) and Control (n = 55) | 8 (14.55) | 9.98 ± 1.78 | 0.002 |
| Schizophrenia (36–50 years) (n = 30) and MDD (36–50 years) (n = 10) | 4 (40) | 86.17 ± 26.84 | 0.352 |

* Significant difference if P < 0.05.
middle (26–35 years) and oldest (36–50 years) groups respectively. Toxoplasma positivity rate was highest (40%) among the oldest group of MDD patients followed by the middle-aged one (31.58%). Mean IgG values were significantly higher in middle and oldest age groups, among both schizophrenic and MDD patients, compared to their correspondents in the control group (Table 3).

Relevant family history, of a psychiatric disorder, was studied as a covariate that might reflect both genetic and environmental factors influencing the association between toxoplasmosis and schizophrenia and/or MDD. The results showed that the incidence of toxoplasma positivity, while high in all psychiatric groups, was almost evenly distributed in both family-history positive and family-history negative groups. The results showed also that the high anti-Toxoplasma IgG values were evenly distributed in schizophrenia and MDD groups regardless of the presence or absence of a relevant family history with no significant influence of family history on IgG mean values in both groups (Table 4).

The prevalence of specific anti-Toxoplasma IgM antibodies was rare. Out of a total of 177 serum specimens examined (patients and control), only three patients were positive for IgM antibodies. Surprisingly, all three IgM-positive cases were belonging to the schizophrenic group of patients with an incidence rate of 4.76%.

4. Discussion

The current study has presented serological evidences that link latent toxoplasmosis with two common psychiatric disorders, schizophrenia and MDD. The association of Toxoplasma infection with psychiatric diseases has been increasingly acknowledged in the past two decades. Epidemiological as well as serological evidences have, recently, strengthened the suggestion that Toxoplasma infection might mediate some psychiatric disorders especially schizophrenia [26]. Earlier studies indicated that serologic positivity for toxoplasmosis is almost three times higher in schizophrenic patients than in healthy individuals living in the similar geographic area [14,31,32]. T. gondii seropositivity, in another study, was 2.73 times more common in schizophrenic patients than in healthy individuals [33]. There is also serological evidence that the parasite may be involved in the development of Alzheimer’s [34], Parkinson’s disease [35] and epilepsy of unknown etiology [36].

Many mechanisms have been suggested to link T. gondii to psychiatric disorders. Toxoplasma infection, principally in schizophrenia, represents a main environmental trigger mediating the interaction between personal vulnerability, genetic milieu, neurotransmission and modulation of the immune system [29]. The neurotransmitters link is the most acceptable theory. T. gondii has a specific tropism for brain tissue manipulating the neurotransmitters relevant to some psychiatric disorders [37,38]. Indoleamine 2,3-dioxygenase, that downregulates serotonin, has been reported to be induced by toxoplasma infection [29,37]. T. gondii genome contains genes encoding tryptophan hydroxylase, that upregulates the synthesis of dopamine [37,39]. The association of toxoplasmosis with schizophrenia is purportedly due to dopamine dysregulation and dopaminergic signaling modification by the parasite. Some researchers have suggested that hyperactive dopaminergic signal transduction may play a role in the pathophysiology of schizophrenia [25].

Hypotheses, other than simple infection or neurotransmitter theory, could be proposed to connect toxoplasmosis and psychiatric disorders. T. gondii has a special affinity for microglia [18], now thought to be centrally involved in the schizophrenia pathogenesis [22]. An interesting finding states that some drugs, used to treat schizophrenia, have the ability to hamper the replication of Toxoplasma in culture [40]. Another consideration linking toxoplasma infection to psychiatric disorders is the fact that Toxoplasma infection induces a host’s immunological environment with mounting oxidative stress characterized by overproduction of toxic free radicals like reactive oxygen species and nitric oxide [41], involved in the pathophysiology of many psychiatric and neurodevelopmental disorders [10].

Table 3
Toxoplasma positivity rate and IgG values among different gender groups.

| Paired groups                        | Toxo positivity (No./%) | IgG level (IU/ml) (Avg. ± SD) | P-value* |
|--------------------------------------|-------------------------|--------------------------------|-----------|
| Schizophrenia (males) (n = 55)       | 18 (32.37)              | 185.54 ± 57.24                 | 0.004     |
| and Schizophrenia (females) (n = 8) | 2 (25)                  | 64.69 ± 26.38                  |           |
| MDD (males) (n = 18)                 | 6 (33.33)               | 216.35 ± 69.78                 | 0.001     |
| and MDD (females) (n = 21)          | 4 (19.05)               | 49.58 ± 21.94                  |           |

* Significant difference if P < 0.05.

Table 4
Toxoplasma positivity rate and IgG values in relation to relevant family history.

| Paired groups                          | Toxo positivity (No./%) | IgG level (IU/ml) (Avg. ± SD) | P-value* |
|----------------------------------------|-------------------------|--------------------------------|-----------|
| Schizophrenia with +ve family history  | 6 (35.29)               | 81.28 ± 19.68                  | 0.078     |
| and                                   |                         |                                |           |
| Schizophrenia with −ve family history  | 14 (30.43)              | 63.05 ± 18.15                  |           |
| (n = 46)                               |                         |                                |           |
| MDD with +ve family history (n = 11)   | 3 (27.27)               | 49.86 ± 12.64                  | 0.086     |
| and                                   |                         |                                |           |
| MDD with −ve family history (n = 28)   | 7 (25)                  | 67.63 ± 17.57                  |           |

* Significant difference if P < 0.05.
The current study is one of few studies, tried to explore a possible link between toxoplasma infection and MDD. On the contrary of our results, most of these earlier studies showed no significant associations between *T. gondii* sero-prevalence and major depression [29,42]. A possible role of toxoplasma infection in the causation of depression was suggested in another study [28].

The surprising results of the current study, of low toxoplasma positivity rate and insignificant IgG levels in the youngest age group, together with almost absence of IgM prevalence, could suggest an absent role of primary or reactivated infections in the pathogenesis of schizophrenia and/or MDD. Antibody titer is considered as an inverse correlate of the duration of infection, with the intensity of personality changes became more evident as the duration of infection increased [20]. Absence of IgM antibodies in older study groups, further confirms a prevailing impression that primary infection was unlikely to be a cause of schizophrenia [12]. All our results conform to a final conclusion that latent infection, perhaps going back to the prenatal era, is the phase of toxoplasmosis that favors the development of schizophrenia and/or MDD. A broad-scale detection of IgM in a larger study might help to verify our finding.

Relevant family history has no obvious additive role, according to our results, in predisposing schizophrenia and MDD. Surprisingly, toxoplasmosis seems to, solely, orchestrate the pathophysiology of those illnesses. This finding contradicts the etiologically heterogeneous nature of psychiatric disorders that is believed to have a strong genetic and environmental background [2]. This finding could explain why members of the same family that have a common genetic background and living in the same environment have different susceptibilities to develop a psychiatric disorder. It might also suggest that infection might interact with risk factors, other than genetics, to precipitate such illnesses.

The “gender factor” had an obvious influence in our results where, both the *Toxoplasma* positivity as well as the IgG values were significantly higher in male patients of all psychiatric groups. Latent toxoplasmosis impairs the psychomotor performance of human subjects and affects the human personality profile with an obvious gender difference [43]. Female sex hormones are known to manipulate the dopaminergic actions in certain parts of the brain [44] exerting a protective action on dopamine causing a lower incidence of degenerative disorders in women such as parkinsonism [45]. Thus, our finding could be due to the protective effect of female sex hormones on dopamine, a molecule that has long been suggested to be principally manipulated by *T. gondii* to induce such disorders [37]. Higher levels of testosterone in males could be responsible for at least some of the toxoplasmosis-associated shifts in human and animal behavior [46].

5. Conclusion

The findings, of the current study, add to a mounting number of reports suggesting a link between infections, known to disrupt fetal neurodevelopment, and the risk of neuropsychiatric disorders especially schizophrenia. In addition it suggests a possible role of toxoplasmosis in the development of major depression which is a poorly developed area with scarce scientific reports.

Conflict of interest

The authors declare that there is no conflict of interest.

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