



Original Article

Serological evidences link toxoplasmosis with schizophrenia and major depression disorder



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ARTICLE INFO

Article history:

Received 1 March 2015

Accepted 31 March 2015

Available online 16 April 2015

Keywords:

Toxoplasmosis

Schizophrenia

Depression

Age

Gender

ABSTRACT

The etiology of psychiatric disorders is largely unknown. A role of environmental insults during early neurodevelopment have been suggested. Infections are possible risk factors for psychiatric disorders especially *Toxoplasma gondii*, a neurotropic parasite with a life-long residence in brain. This study has investigated a possible role of toxoplasmosis in the development of schizophrenia and major depression disorder (MDD). The influence of other covariates; age, gender and family history was also studied. A cross-sectional study on a total of 177 individuals, where anti-*Toxoplasma* IgG and IgM in sera of schizophrenia ($n = 63$) and MDD ($n = 39$) patients, all fulfilling DSM-5 diagnostic criteria, were compared to healthy volunteers ($n = 55$). *Toxoplasma* positivity was highest (31.75%) among schizophrenics followed by MDD (25.64%) and controls (14.55%). IgG levels were significantly higher in toxo-positive schizophrenics (230.1 ± 22.9) and MDD (220.56 ± 24.8) compared to controls (9.98 ± 1.78). Three patients only, all schizophrenic, have positive IgM antibodies. Age and male gender appear to have positive associations to toxoplasmosis and psychiatric disorders while family history has no obvious additive role. This report is one of few linking *Toxoplasma* infection to MDD and adds to many suggesting a link between latent toxoplasmosis and schizophrenia.

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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

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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 anti-toxoplasma IgG and IgM using commercially available ELISA kits (NovaTec Immundiagnosics 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 $\times 10/\text{cut-off}$. IgM levels ≥ 11 NTU/ml were considered positive.

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