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Toxoplasma Antibody Titers in Mania: A Cross Sectional Study

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Abstract:

Background: Recent studies have found a role of infectious agents, especially *Toxoplasma gondii*, in pathology of bipolar disorder - mania. *Aim and Objectives*: This study was conducted with the aim to find the prevalence of toxoplasma antibody titers in Indian patients with mania and to assess its specificity towards the clinical profile. *Material and Methods:* Thirty-four patients having mania were recruited who were psychotropic naïve/free, along with 74 healthy controls. Psychopathology was assessed using structured assessment scales. Serum concentration of Toxoplasma IgG was measured using Diesse Enzywell Toxoplasma IgG immunoassay kit. *Results:* Mann–Whitney U test revealed that the toxoplasma antibody levels were significantly higher in the mania group than healthy controls ($U = 766.5$, $z = 3.25$, $p = 0.001$). Spearman correlation analyses did not reveal any significant correlation between toxoplasma antibody levels and age at onset ($\rho = 0.19$, $p = 0.26$) or YMRS scores ($\rho = 0.15$, $p = 0.39$). *Discussion:* The herein reported association could have potential implications in better understanding the patho-physiology of mania and its treatment. This is the first study to evaluate the association between toxoplasma titers and mania in India with only a few studies done elsewhere in the world.

Keywords: Bipolar, Mania, Psychosis, Toxoplasma

Introduction:

Bipolar Disorders (BD) are a group of psychotic disorders of as yet uncertain etiology, characterized by episodes of mania and depression. Genetic variations have a major underlying role to play in the susceptibility and pathogenesis of BD, but the exact molecular mechanisms are yet to be fully ascertained [1]. Recent study found a role for both infection and inflammation in pathology of BD which is contingent upon genetic variations [2]. Among the infectious agents, *Toxoplasma gondii* has received lot of research interest recently as a causative agent for a number of psychiatric disorders [3].

T. gondii is a ubiquitous parasite found in a variety of hosts. It is increasingly being recognized as a global threat [4]. It is one among many parasites which have been found to alter the host behaviour [5,6]. There is only one species, *gondii* in the genus toxoplasma. Different strains of *T. gondii* have been identified which employ different strategies to avoid, deflect or subvert host defense mechanisms [7]. It can inhabit and multiply in all nucleated cells [8]. It has two phases during replication, each occurring in different hosts – a sexual phase in cats and an asexual phase in other hosts. Humans are infected when exposed to cat

feces or upon consumption of poorly cooked meat and unpasteurized goat milk [9]. *T. gondii* oocysts are also found on vegetables, fruits and in water, resulting in an increased risk of infection among vegetarians/ vegans [10]. Additionally *T. gondii* could be transmitted from person to person by modes of mother-to-child transmission, organ transplantation and rarely by blood transfusion [11,12].

Sero-positivity for anti-toxoplasma IgG antibodies is the marker for asymptomatic human infection. However, when the prevalence of such infection is evaluated, significant variations are noted across the globe, from 47% in rural France to 6.7% in Korea [13]. These variations are likely to be reflections of cooking methods, levels of cleanliness and climactic conditions among the populations studied. A study in India (2007), also demonstrated the wide differences in the prevalence of *T. gondii* sero-positivity between various states in India. It found an average prevalence of 24.3% of *T. gondii* IgG antibodies with lowest sero-prevalence in the north Indian state of Rajasthan (9.4%) and highest (48.2%) in the south Indian state of Kerala [14]. This vast difference could possibly be accounted by the negative impact of arid climatic conditions on the survivability of *T. gondii* oocysts in northern India.

An interesting phenomenon in laboratory mice called the *fatal feline attraction* highlights the propensity of *T. gondii* to infect the central nervous system, especially the limbic structures, olfactory bulbs, entorhinal, somatosensory and motor cortices [15,16]. This phenomenon is characterized by *T. gondii*'s manipulation of rat's perception of cat predation risk by turning their innate aversion to cat urine into an imprudent attraction [17]. Interestingly similar phenomenon has also been observed in *T. gondii* infected humans [18]. Recent studies have found that *T. gondii* may also invade and replicate within astrocytes [19]. All these studies suggest a neuro-anatomical basis for the behavioral changes associated with *T. gondii* infection.

T. gondii produces tyrosine hydroxylase, an enzyme necessary for the synthesis of dopamine, which has been detected in high concentrations in infected neurons *in-vitro* and *in-vivo* [20]. *T. gondii* can directly increase dopamine production as the parasite synthesizes an enzyme tyrosine hydroxylase, belonging to the family of Aromatic Amino Acid Hydroxylases (AAH), involved in dopamine production [21]. Dopamine is well-recognized to influence mood and cause psychosis [22,23]. These findings highlight the neuro-chemical basis for *T. gondii* induced behavioral alterations.

Coming to specific alterations in behaviour, research has found schizophrenia, depression and suicidality to have links with *T. gondii* infection [24-27]. The link between depression and *T. gondii* infection is strengthened by the finding that treatment-resistance in depression is overcome by treating the infection [28]. A recent systematic review and meta-analysis of research done world over found an odds ratio of 1.81 and 1.52 for schizophrenia and bipolar disorder, respectively, indicating a substantial association with *T. gondii* infection [3]. Elevated anti-toxoplasma IgM and IgG levels have been noted in patients with bipolar disorder [29,30]. Further a large population based sample found elevated *T. gondii* seroprevalence in bipolar disorder only and not in unipolar mood disorders [31].

Psychotropic drugs especially haloperidol and valproic acid, have been found to exert anti-

parasitic actions, not unlike standard drugs like pyrimethamine and Dapsone (DDS). This effect may be explained by the inhibition of replication of tachyzoites observed in cell culture studies [32,33]. In turn, this novel mechanism may provide one more mechanism by which antipsychotics and mood stabilizers bring about improvement in behaviours in illnesses like schizophrenia and mood disorders [34].

Taking these aspects in perspective, we conducted this study to identify an association of *T. gondii* antibody titers in psychotropic-naïve/ free patients with bipolar disorder – mania in comparison to healthy controls. We hypothesized that the *T. gondii* IgG antibody titers will be significantly higher in patients with mania in comparison to healthy controls and there will be a significant association of the antibody titers with the symptom severity in mania.

Material and Methods:

Clinical Profile

This was a cross-sectional study conducted over a period of 12 months at National Institute of Mental Health and Neurosciences (NIMHANS) located in the southern Indian state of Karnataka. Thirty-four patients having mania were recruited after satisfying the following criteria:

Cases	
Inclusion Criteria	**Exclusion Criteria**
1) Diagnosis of BD – Manic episode based on ICD-10 criteria 2) Psychotropic-naïve/ free status 3) Actively ill 4) Age range: 18 – 45 years, 5) Both sexes	1) Features suggestive of risk of harm to self (for example: suicidal risk, catatonia, prolonged nutritional deprivation) or others (for example: aggression or excitement) 2) Recent history of high grade fever/infection within the past 6 weeks 3) Co-existing disease that can potentially influence immune system (immune-compromised states, autoimmune diseases like rheumatoid arthritis, cancer and similar others) 4) Treatment with medications known to affect immune systems (COX-2 inhibitors, steroids, anti-inflammatory agents and similar others) 5) Pregnancy or postpartum 6) Significant neurologic disorder

Seventy-four matched healthy controls were recruited after satisfying the following criteria:

Controls	
Inclusion Criteria	**Exclusion Criteria**
1) Age range: 18 – 45 years 2) Both sexes and 3) Written informed consent	1) Diagnosis of a psychiatric disorder 2) Other exclusion criteria similar to cases as mentioned above.

The details related to psychotropic-naïve or psychotropic-free status was ascertained by reliable information obtained from at least one first degree relative. Institutional (NIMHANS) Ethics Committee approval was taken prior to recruiting the patients. The clinical and immunological assessments were done in all subjects after taking written informed consent in English/Hindi/Kannada.

The demographic and clinical information of patients were collected with the help of structured scales and proforma. The diagnosis was established clinically using the Mini International Neuropsychiatric Interview Plus which was confirmed independently by a qualified psychiatrist [35]. Psychopathology was assessed using Young Mania Rating Scale [36].

Blood Sample Collection and *T. gondii* IgG immunoassay

Five millilitres of blood was drawn from ante-cubital vein and collected in BD Vacutainer® Brand SST™ Tubes containing silica and gel. The serum was separated within two hours of sample collection and stored at -80°C until analysis. *T. gondii* IgG levels were determined using a quantitative sandwich enzyme immunoassay kit (DIESSE Diagnostica Senese, Italy) according to manufacturer's directions. This ELISA kit was highly specific for *T. gondii* IgG antibody. The assay standard range was up to 200 IU/mL. All samples were coded, thawed only once and analyzed by the investigators who were blind to the clinical situation. Calibrators, assay controls and 10% of the test samples were run in duplicates. Assays were validated using negative control and cut-off [8 IU/mL] control. Replicates showed 100% concordance on the degree of immunity.

Statistical Analysis

Statistical analyses were performed using the IBM Statistical Package for Social Sciences software version 15 for Windows. Comparison of demographic characteristics was done using independent samples T-test for continuous variables and chi square test for categorical variables. Since the *T. gondii* antibody levels were not normally distributed within each diagnostic group; the analyses were performed using Mann–Whitney U test, a rank-based nonparametric test. Correlation analysis was performed using Spearman's correlation.

Results:

Demographic details of both groups are presented in Table 1.

Table 1: Clinical and Demographic Variables

Characteristics	Patients	Controls	Statistic	p
N	34	74	-	-
Age (years)	32.8 ± 6.84	26.61 ± 4.72	2.69*	0.01
Sex (M:F)	19:15	47:27	0.57[#]	0.52
Age at onset (years)	24.97 ± 8.14	-	-	-
YMRS total	27.12 ± 7.16	-	-	-
T. gondii IgG (Median IU/ml)	11.9 ± 29.4 (.37)	.40 ± .57 (.24)	3.251 [$]	0.001

**independent samples t-test, [#]chi-square test, [$]Mann–Whitney U test*

There was a significant difference among the ages of the diagnostic groups (independent samples T-test, t = 2.69, P = 0.01). Chi square test revealed no significant difference in sex distribution across groups, ($\chi 2$ = 0.57, P = 0.52). Mann–Whitney U test revealed that the *T. gondii* antibody levels were statistically significant different between groups (U = 766.5, z = 3.25, p = 0.001). Patients with mania showed a significantly higher concentration than healthy controls. Spearman correlation analyses did not reveal any significant correlation between *T. gondii* antibody levels and age at onset (ρ = 0.19, p = 0.26) or YMRS scores (ρ = 0.15, p = 0.39). We did not find any association between the antibody titers with patients' family history of BD.

Discussion:

This study demonstrated that there is a significant association between *T. gondii* antibody titers and mania. To the best of authors' knowledge this is the first such study in India. This finding replicates the finding of Hamdani *et al*., (2013) where it was found that the sero-positive group for IgG antibodies to *T. gondii* had a 2.7 fold odds of having bipolar as compared to sero-negative group [30]. Similarly Pearce *et al*., (2012) also demonstrated an increased risk for bipolar disorder in *T. gondii* infected individuals [31]. Further a recent systematic meta-analysis found that *T. gondii* infection may be associated with several psychiatric disorders including BD [3]. Raised anti-*T. gondii* IgM levels, and not IgG levels, have also been documented in BD [29]. Similarly significantly higher *T. gondii* seropositivity was found in a recent study which also evaluated their cognitive status and IL-6 levels [37].

Such inconsistent observations can be explained by 3 mechanisms: 1) differential localization of *T. gondii* within CNS may bring about location specific behavioral changes [15,16,19]; 2) host specific differential sensitivity and activation of immune system may result in host specific behavioral changes, eg., CD4 and CD8 cells secrete a plethora of cytokines in response to *T. gondii* infection which itself is dependent on a subtle interplay between host and parasite genotypes leading to considerable variation in observed immune profile and course of infection [38]. Such chronic immune activation has been known to alter the brain neurotransmitters responsible for a host of psychiatric disorders including schizophrenia and bipolar disorder [39]; 3) the type of antipsychotics and mood stabilizers used could bear an immense impact on the *T. gondii* titers [32].

Further, the observed significant association between mania and *T. gondii* infection could be multi-factorial: 1) *T. gondii*'s propensity to infect limbic structures could lead to disruption of frontal-limbic functional neuro-anatomical network which has been implicated in BD [15,16,40]; 2) *T. gondii*'s invasion and replication within astrocytes could lead to deficient astroglial function which is believed to contribute to overall disbalance in neurotransmission and pathological evolution of BD [19,41]; 3) increased production of dopamine by *T. gondii* can also play a central role in BD psychopathology [20,21,42]; 4) *T. gondii* infection leads to neuro-inflammation and resultant increase in inflammatory cytokines like IL-6 [43]. Increased levels of IL-6 have been consistently observed in BD and could be responsible for some of the symptoms observed in mood disorders [44].

We did not find any significant association between sero-positivity and symptom severity as assessed using standardized scales. This is in

contrast to the study which found that latent toxoplasmosis may lead to more severe positive psychopathology and perhaps less favorable course, albeit in schizophrenia [45]. Similarly, no association was noted between the demographic and clinical characteristics of *T. gondii* sero-positive and sero-negative patients in a French study [30]. On the other hand, with respect to only cognitive symptoms, one study involving 42 patients found significantly higher cognitive deterioration index among patients with BD which correlated with their IL-6 levels [37]. The possible reason for different findings obtained from studies of *T. gondii* with BD and other psychiatric disorders around the world could also be related to the genotype of *T. gondii* which vary in virulence based on geographical location [46]. The distinct neuro-pathogenic potential has been known in different genotypes of *T. gondii* [7].

The present study was conducted to evaluate the association between *T. gondii* infection with mania. This is the first study to evaluate the same in India with only a few studies done elsewhere in the world. Moreover, the study was conducted in psychotropic-naïve/free patients with mania to rule out the confounding effect of psychotropics on antibody titers [32,33]. Despite these, the study has its inherent limitations. First of all the study is of cross-sectional design with no longitudinal component looking at the changes in antibody titers with treatment. Food habits are known to influence the chances of exposure to *T. gondii* and possibly its subsequent antibody levels, which were not controlled in this study [9,10]. Further, the results can't be generalized since the seroprevalence is not the same across India [14]. BD patients with depression were not included. Finally, IgM levels were not evaluated because we were looking for long term biomarker of infection. The herein reported association between mania and *T. gondii* infection will have potential implications on understanding the psychopathology of BD and mania along with its treatment. Indeed adequate treatment of infection by *T. gondii* was reported to improve the efficacy of antidepressant treatment and treatment of BD patients with psychotropic drugs having inherent anti-toxoplasma activity improved their clinical profile [28,34]. Although our results are to be interpreted with caution because of the small sample size, they do raise the possibilities of developing therapeutic strategies that take into account the immuno-inflammatory and serological status of patients with BD in the future. But at the same time, our lack of correlation between *T. gondii* infection and symptom severity warrants further investigation. Numerous factors need to be taken into consideration before concluding *T. gondii* as a common denominator for multiple neuropsychiatric disorders. Although the evidence has been gradually accumulating, we could just be touching the tip of the iceberg in terms of our understanding about *T. gondii* infection and its varied manifestations paving the way for more rigorous and large-scale studies in the future.

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