Psychiatric aspects of toxoplasmosis: an Indian perspective

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Abstract *Toxoplasma gondii* is one of the well-studied parasites because of its medical and veterinary importance, and its suitability as a model for cell biology and molecular studies. Latent toxoplasmosis in an immunocompetent host was considered benign until recently. The importance of this parasite has been steadily rising in the field of psychiatry and neurology as it has been implicated in numerous neuropsychiatric disorders. Researchers in India have unfortunately restricted themselves to finding the prevalence of toxoplasma antibodies in special populations and animals. On the other hand, there has been increasing research interest worldwide in *T. gondii* for its effects on human behaviour, manifestations of which range from psychoses and neuroses to Alzheimer's and Parkinson's disease. *Toxoplasma* infected organisms may be akin to living zombies. From changing the core natural defensive behaviour in mice to changing personality & leading to neuropsychiatric disorders in humans, *Toxoplasma* brings about subtle but significant & specific changes in its host. Surprisingly there is severe dearth of such studies from India even though prevalence rates of latent *Toxoplasma* infection are comparable, or in some regions, higher to those found elsewhere in the world. The potential for identifying *Toxoplasma* induced behavioural alterations is enormous in this part of the world which could have future treatment implications. It's high time that we move beyond

researching the obvious and involve ourselves in more rigorous, novel and stimulating studies in the future.

Keywords Psychiatry · Behavioral · Psychosis · *Toxoplasma* · India

Toxoplasma gondii is one of the well-studied parasites because of its medical and veterinary importance, and its suitability as a model for cell biology and molecular studies. The importance of this parasite has been steadily rising in the field of psychiatry and neurology as it has been implicated in numerous neuropsychiatric disorders. There has been increasing research interest in *T. gondii* for its effects on human behavior, manifestations of which range from psychoses and neuroses to Alzheimer's and Parkinson's disease. The author had initially tried to do a systematic review of research done in India linking *Toxoplasma* to various behavioral manifestations in humans but surprisingly there is severe dearth of such studies even though prevalence rates of latent *Toxoplasma* infection are comparable to those found elsewhere in the world. Hence the focus of this paper was shifted to perform a brief review of research done worldwide on *Toxoplasma* induced behavioral manifestations and thereby stimulate interest among Indians to perform research in this exciting albeit speculative field.

Although *T. gondii* has a worldwide distribution and perhaps the widest host range of any parasite, there is only one species, *gondii* in the genus *Toxoplasma*. It is capable of infecting and replicating within virtually any nucleated mammalian or avian cell. Its life cycle is divided between feline and nonfeline infections, which are correlated with sexual and asexual replication, respectively. Major routes of human *T. gondii* infection worldwide are through

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exposure to feline feces and ingestion of raw or improperly cooked meat. In India, where vegetarianism is predominant, ingestion of drinking water, or raw fruits and vegetables contaminated with *T. gondii* oocysts, is a likely source of human infection (Hall et al. 1999).

Researchers in India have unfortunately restricted themselves to finding the prevalence of *Toxoplasma* antibodies in special populations and animals. A PubMed search with the terms ‘*Toxoplasma*’ and ‘India’ returned back 182 results (as on 10th June, 2014) without even a single paper on behavioral manifestations of toxoplasmosis. The prevalence of asymptomatic human infection as reflected by seropositivity for IgG anti-*T. gondii* antibodies varies considerably across the globe, from 4.1 % in Thailand to 82.5 % in Brazil (Sundar et al. 2007). In India, the seroprevalence was found to be 24.3 % with lowest in the Northern state of Rajasthan (9.4 %), and the highest (48.2 %) in the South Indian state of Kerala (Dhumne et al. 2007).

Acute *Toxoplasma* infection is generally seen in immunocompromised patients and expectant mothers leading to congenital toxoplasmosis. Latent toxoplasmosis in an immunocompetent host was considered benign until recently. *Toxoplasma* has tropism for the central nervous system but it remains to be seen whether it localizes to specific brain regions. Recent work provides a potential process for fatal feline attraction in mice mediated by pathways that activate the amygdala (House et al. 2011), which seems a plausible explanation since amygdala is considered to be the seat of emotional memory.

A variety of behavioral manifestations have been observed in individuals having latent toxoplasmosis which include personality disturbances (Hodková et al. 2007) and even schizophrenia. A meta-analysis of 23 studies found an increased prevalence of *Toxoplasma* antibodies in patients with schizophrenia (Torrey et al. 2007). The reasons why only a proportion of individuals that have been infected with *Toxoplasma* develop behavioral manifestations are unclear. Possibilities include differences in genetic susceptibility, mode of infection (tissue or oocytes), and/or timing of infection (in utero, childhood or adulthood). Alternatively it has been suggested that behavioural traits associated with schizophrenia could result in increased infection with the parasite. For example, the transmission of the parasite could be related to a lack of personal hygiene. However, this is unlikely to explain all cases, and since *Toxoplasma* encysts in the brain, there is a clear potential to affect neuronal function directly. In order to clear this dilemma, one group examined banked blood specimens from the U.S. military to determine rates of previous infection in new-onset schizophrenia within the military and found significant association between antibody level and risk of schizophrenia, indicating that

T. gondii could be considered one factor contributing to the illness (Niebuhr et al. 2008). In fact, the chances of *Toxoplasma* being the causative/contributory factor in the development of schizophrenia has been found to be more than that of genetic and environmental factors (Torrey et al. 2007). Maternal exposure to *Toxoplasma* may also be a risk factor for schizophrenia in their offspring (Brown et al. 2005). Given that Toxoplasmosis is a preventable infection, this could have important implications in reducing the incidence of schizophrenia through prenatal test and education.

There is emerging evidence that *Toxoplasma* infection can cause depression in certain individuals. For example, the incidence of *Toxoplasma* infection as determined by serology was greater in depressed patients compared with a control group in one of the older studies (Delgado and Perdomo 1980). Furthermore in a rare case report emerging from India, a patient who was unresponsive to conventional antidepressants, when treated for an underlying *Toxoplasma* infection, the depression was ameliorated (Kar and Misra 2004). Few studies have demonstrated an increase risk for bipolar disorder in *toxoplasma* infected individuals (Pearce et al. 2012). An increased association has also been found in people with suicidal behavior (Okusaga and Postolache 2012). A very new area of possible linkage is that of *T. gondii* to Alzheimer’s disease (Kusbeci et al. 2011). *T. gondii* has also been demonstrated to contribute to the formation of certain types of brain tumours (Ryan et al. 1993), decreased IQ (Flegr et al. 2003) and psychomotor performance (Havlicek et al. 2001). Increased incidence of seropositivity has also been reported in patients with obsessive–compulsive disorder (Miman et al. 2010), parkinsonian symptoms (Murakami et al. 2000), Tourette’s syndrome (Krause et al. 2010) and autism spectrum disorders (Prandota 2010).

The mechanism of behavioral alteration has been found to be primarily through alteration in the neurotransmitter dopamine as the parasite synthesizes an enzyme tyrosine hydroxylase, involved in its production (Gaskell et al. 2009). Host immune system activated by *Toxoplasma* has also been found to alter neurotransmitter levels. Immune reaction against *Toxoplasma* is complex involving both innate and specific immunity including B-cells & T-cells (Aosai et al. 2006). Along with systemic effects, *Toxoplasma* induces the production of a number of cytokines directly within the brain (Schlüter et al. 1997). These cytokines may influence mood and behavior through their ability to modulate neurotransmission. Interferon has been found to mediate effects like sickness behavior and even depression (McCusker and Kelley 2013).

Evidence for the role of *Toxoplasma* in behavioral modulation is also seen indirectly. Certain antidepressants (Hinze-Selch et al. 2000) and antipsychotics (Schuld et al.

2000) modulate cytokine systems some of which get abnormally activated following *Toxoplasma* infection as explained above. There are also similar reports on mood stabilizing agents such as lithium (Rybakowski 2000), valproate (Queiroz and Mullen 1992) and carbamazepine (Furst and Uetrecht 1995). Studies have demonstrated that *T. gondii* antibodies of schizophrenia patients treated with anti-psychotic drugs are intermediate between those of patients never treated and those of control groups, with a significant further reduction in those patients undergoing current drug treatment. This is supported by the observation that many anti-psychotic drugs commonly used in the treatment of schizophrenia inhibit the replication of *T. gondii* tachyzoites in cell culture (Jones-Brando et al., 2003). Interestingly, haloperidol and valproic acid have been shown to have anti-toxoplasma activity which is equivalent to effect produced by standard anti-toxoplasma drugs such as pyrimethamine with dapsone (Webster et al. 2006). One could, therefore, conclude that the anti-psychotic and mood stabilizing activity of some medications may be achieved, or at least augmented, through their inhibition of *T. gondii* replication and invasion in infected individuals. Alternatively those seropositive patients who are unresponsive to standard antipsychotic medications may be shifted to the above drugs with established anti-toxoplasma activity thereby giving a new ray of hope for treating chronic resistant psychiatric disorders.

From the accumulated evidence so far, it appears that *Toxoplasma* infected organisms may be akin to living zombies. From changing the core natural defensive behavior in mice to changing personality & leading to neuropsychiatric disorders in humans, *Toxoplasma* brings about subtle but significant & specific changes in its host. It is difficult to ascertain the significance of the behavior change seen in *Toxoplasma* infected humans considering we are dead end hosts for *Toxoplasma*. There is burgeoning evidence coming from the western world, but India is lagging behind. The author himself has done preliminary research to find an association between *Toxoplasma* and different forms of psychoses which is still in the process of publication. NMDA encephalitis presenting with psychotic symptoms has generated a wave of interest all over the world with interesting case reports from India. The author hopes to generate similar interest in psychiatric manifestations of *T. gondii*. Considering the comparable or in some regions, higher prevalence of *toxoplasma* in India as compared to other parts of the world, the potential for identifying *Toxoplasma* induced behavioral alterations is enormous. It's high time that we move beyond researching the obvious and involve ourselves in more rigorous, novel and stimulating studies in the future.

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