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Review article

Neurobiological studies on the relationship between toxoplasmosis and neuropsychiatric diseases

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ABSTRACT

Toxoplasma gondii is a widespread protozoan parasite infecting approximately one third of the world population. After proliferation of tachyzoites during the acute stage, the parasite forms tissue cysts in various anatomical sites including the Central Nervous tissue, and establishes a chronic infection. Clinical spectrum normally ranges from a completely asymptomatic infection to severe multi-organ involvement. Many studies have suggested *T. gondii* infection as a risk factor for the development of some neuropsychiatric disorders, particularly schizophrenia. During the last years, a potential link with other neurobiological diseases such as Parkinson disease and Alzheimer disease has also been suggested. This review will focus on neurobiological and epidemiological data relating infection with *T. gondii* to neuropsychiatric diseases.

Contents

1. Introduction

Toxoplasmosis is a widespread parasitic disease caused by *Toxoplasma gondii*, an obligate intracellular protozoa belonging to the phylum Apicomplexa with a complex life cycle and humans as intermediate host, in which, after proliferation of tachyzoites during the acute stage, the parasite forms tissue cysts in various anatomical sites, including the brain, and establishes a chronic or latent lifelong persistent infection [1].

Clinical spectrum, in the immunocompetent individuals, ranges from a completely asymptomatic infection or negligible symptomatic forms to, very infrequently, severe multi-organ involvement [1,2].

Parasite factors (*inoculum* size, timing, strain, virulence) and host factors, such as genetic background, sex, and immunological status, seem to affect the course of infection in human being [1]. Studies of gene sequencing have identified different genotypes (the classical I, II,

Abbreviations: CNS, Central Nervous System; DOPA, dopamine; D_2R, DOPA receptor; GABA, gamma-aminobutyric acid; HPA, hypothalamic–pituitary–adrenal; IDO, indoleamine 2,3-dioxygenases; IFN, interferon; IL, interleukin; IS, immune system; KYNA, kynurenic acid; L-KIN, L-kynurenine; NMDA, N-methyl D-aspartate; TDO, tryptophan 2,3-dioxygenase; TH, tyrosine hydroxylase; Th1, Th2, T helpers 1 and 2; TRP, tryptophan.

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III, as well as recombinant and exotic genotypes) with different clinical manifestations. However, re-infection with genotypes other than those of a primary infection is also possible [3].

Many studies suggested toxoplasmosis as a risk factor for the development of behavioral changes and neuropsychiatric disorders, although a clear etiopathogenetic link has not yet been established. Particularly data focus on the interrelationships of *T. gondii* infection with schizophrenia, whereas studies on well-characterized psychiatric patients with distinct diagnoses other than schizophrenia have not yet been published so far, to our knowledge.

Now research also begins to evaluate the possible association between exposure to *T. gondii* and development of some neurological disorders such as Parkinson disease [4] and Alzheimer disease [5].

This review focuses mainly on neurobiological data relating infection with *T. gondii* to neuropsychiatric diseases, whereas we have just reviewed, in a recent publication, serological studies on this topic [6].

As regards epidemiological aspects, findings evidence affinities and differences between toxoplasmosis and schizophrenia, as summarized in Table 1.

2. The origins of the infective theory on the etiology of neuropsychiatric disorders

The idea that psychotic disorders might be etiologically related to infectious diseases dates from the late 19th century. Kraepelin first [15], in 1896, postulated that toxins secreted by infectious agents may cause an organic brain pathology. Menninger [16], following the 1918–1919 influenza pandemic, theorized a viral etiology for encephalitis and schizophrenia and only later, attention shifted to parasites, either protozoa or helminths (*Giardia duodenalis*, *T. gondii*, *Plasmodium* spp., *Ascaris* spp., *Trichinella* spp., *Taenia solium*) [17]. Indeed, genetic background does not completely explain the development of neuropsychiatric disorders and it is likely that, in past years, its role in the etiopathogenesis of the disease may have been overestimated [18]. Among the different infectious agents, *T. gondii* has received more attention for its localization in the Central Nervous System (CNS) [9].

3. The role of *T. gondii* on etiopathogenesis of psychiatric disorders

3.1. Neurobiological studies

T. gondii infection determines systemic neurobiological effects which are different during the course of infection, the proliferative (acute phase) and "dormant" (chronic and latent phase) stages and depend on both host and parasite.

Here we focus mainly on aspects involving CNS, potentially dealing to neuropsychiatric diseases (Table 2).

Analyzing the neuropathologenesis of the *T. gondii* infection on the CNS, direct and indirect effects must be considered.

The *T. gondii* strong tropism for the CNS has been shown analyzing both murine and human models. Brain cysts are formed in the whole brain, preferentially in cerebral hemispheres, hippocampus, amygdala [21], basal ganglia, cerebellum, cerebral cortex, brain stem [22], and olfactory bulb [23], and a variety of brain cells can be infected, including neurons, microglia and mainly astrocytes [24].

Encysted *T. gondii* bradyzoites are capable of inhibiting cellular apoptosis, so they can persist in host cells for long periods of time [25]. As cysts grow, the host cell degenerates and may rupture thereby releasing bradyzoites which can differentiate into tachyzoites and invade and kill surrounding cells, if unchecked by the immune system [26].

Especially in non-immunocompetent patients, the neuropathological involvement is serious, sometimes dealing with hydrocephalus, acute necrotizing encephalitis and formation of glial nodules [27,28].

Lesions occurred in the brain can manifest as behavioural symptoms by interfering with brain functions in the region surrounding the lesion via mass effects or paracrine secretions [29].

That is true considering the observation of tissue cysts high concentration in the amygdala and *nucleus accumbens*, dopamine containing limbic brain regions known to be important for motor control (in particular see basal ganglia), motivation, pleasure, addiction, reward, and fear [30,31].

Nevertheless, a recent study on mice shows no clear region dependent cyst distribution within the hippocampus or amygdala, implying that cysts do not directly cause behavioural changes by perturbation of the surrounding tissue [32].

Table 1
Epidemiological findings in support and against a link between toxoplasmosis and schizophrenia.

Factors	Toxoplasmosis	Schizophrenia
Genetic/familial	Increased risk of infection in members of the same family, likely due to interaction between genetic and environmental factors; a trans-placental transmission of the parasite up to 5 generations was showed in mice [7]	Higher risk in first-degree relatives affected, but no single gene involved definitely identified [8]
Age of onset	Seroconversion peak among 15 and 35 years, early among males [9]	Major clinical manifestation among 20 and 30 years, with early onset among males [10]
Seasonal variation	Patients born in winter or spring show a higher probability of contracting infectious diseases, including toxoplasmosis [11]	The birth season (winter or spring) seems to correlate with risk of schizophrenia development [11,12]
Stillbirth	Increased [9]	Increased [9]
Socio-economic status	Lower [9]	Lower [9]
Residence area	Conflicting data exist on the association between prevalence for toxoplasmosis and residence area [9]	An association may exist with being born or living during childhood in an urban area and the onset of schizophrenia [13]
Geographical correlation	No clear association has been shown between prevalence of *T. gondii* antibodies and schizophrenia. Differences (in association of prevalence rates) exist depending on the geographical area. Countries with a low prevalence of anti-*T. gondii* antibodies generally show a low prevalence of schizophrenia. Subjects from Papua, New Guinea, where domestic and wild cats are rare show low (≤2%) prevalence rates for toxoplasmosis and schizophrenia is poorly disseminated. A geographical association, however, is not found in countries such as France, Ethiopia and Brazil, where prevalence rates of toxoplasmosis are high and schizophrenia prevalence is similar to the general population. This may be in relation to the timing of exposure to *T. gondii*, the route of infection, the parasite genotype more frequently found, and the absence of cofactors required for the infection [9]	
Contacts with cats	The seropositivity to *T. gondii* has increased together with the habit of keeping domestic cats; although cat keeping was documented in ancient Egypt, this practice became popular in the mid-eighteenth century and since then it has increased. In particular, it is important the possession of a kitten under the age of one year [9]	A positive correlation between schizophrenia and cat contact, especially during childhood is likely [14]: • Schizophrenic patients show a higher frequency of exposure to cats in childhood (43%) compared to control subjects (34%) • Families in which members later developed schizophrenia or bipolar disorder, were more likely to have owned a cat. The number was higher (52%) during the period from birth up to 13 years old compared to controls (42%)