

NEUROTROPIC PARASITIC INFECTIONS ASSOCIATED WITH PSYCHIATRIC DISORDERS: A REVIEW ARTICLE

By

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Abstract

Psychiatric disorders are a group of disorders characterized by a combination of changes in behavior, disturbed thoughts, emotions, and relationships with others. They are considered the 3rd most common diseases worldwide, after malignancy and cardiovascular diseases, but the etiology of psychiatric disorders is still questionable. Besides, biological, psychological, and environmental factors increased evidence for the role of viral, bacterial, and parasitic infections in the development of some psychiatric disorders. Studies suggested an association between parasites, especially those with neurological tropism and psychiatric disorders. Toxoplasmosis, human African trypanosomiasis, malaria, Chagas' disease, neurocysticercosis, and human toxocariasis are neurotropic parasitosis that has a predilection for central nervous system in different ways, which could be a trigger to develop neuropsychiatric disorders. Neurological and psychiatric sequelae of these infections result mainly from a complex interplay between parasite and host inflammatory and immune response affecting insitu brain neurotransmitters or causing vascular impairment and some work as space occupying lesions. The study reviewed how those neurotropic parasites could be etiological agents for psychiatric and mental disorders.

Keywords: Toxoplasmosis, Trypanosomiasis, Chagas disease, Malaria, Neurocysticercosis, Toxocariasis, Psychiatric disorders, Mental disorders, Schizophrenia, Depressive disorders, Bipolar disorders, Pathogenesis, Etiology.

Introduction

Psychiatric disorders are chronic illnesses that have significant financial costs to patients, families, and societies, include schizophrenia, bipolar disorder, dementia, depression, and other related brain illnesses (Chen *et al*, 2019). More than 25% of individuals in developing countries suffered from one or more mental or behavioral disorders in their lifetime (Daré *et al*, 2019) and in an Egyptian national preliminary study, about 16.93% of the study population also suffered from psychiatric disorders (Ghanem *et al*, 2009).

Toxoplasmosis (Chen *et al*, 2019), malaria, human African trypanosomiasis (Mallewa and Wilmshurst, 2014), Chagas disease (Ozaki *et al*, 2011), cysticercosis (Wiwantkit, 2014) and human toxocariasis (Alvarado-Esquivel, 2013) are neurotropic parasitic diseases that have a predilection to infect the central nervous system (CNS). Due to the persistent and emerging burden of para-

sitic diseases in developing countries, attention was concentrated on these conditions (Elsheikha *et al*, 2016; Vigo *et al*, 2016).

Human brain is shielded by cellular barriers that control the entry of molecules and microorganisms into the brain parenchyma. The blood-brain barrier (BBB), blood-cerebrospinal fluid barrier (BCSFB), and the meningeal barriers are the main barrier systems that protect neurons from blood-borne external insults including infections (Idro *et al*, 2022). Also, parasites adopted a various mechanisms for tissue migration or systemic spread in human body (Gazzinelli *et al*, 2014). While some parasites could cause acute neurological damage that would be fatal, others' ability to adapt to the human host also made it possible for chronic, and perhaps lifelong, CNS infection (Maizels *et al*, 2018). Therefore, for a parasite to infect the CNS, it must first get passed brain's cellular barriers and then be able to evade the immu-

ne responses that are specific to CNS. Clinical CNS symptoms were frequently linked to processes that arise from the unique host-parasite interaction, which is still poorly understood (Idro *et al*, 2022).

The current study aims to review the association of parasitic infections, particularly those with neurological tropism with various human neuropsychiatric disorders; and how it could be elicited by such infections.

1- Toxoplasmosis: Toxoplasmosis is a highly prevalent zoonosis. Immunocompromised and congenitally infected patients were found to be particularly vulnerable to disease's fatalities (Elsheikha *et al*, 2009; Mohamed and Hajissa, 2016). Its causative agent, *T. gondii*, is an obligatory intracellular eukaryotic protozoan parasite (Tyebji *et al*, 2019). Its genotypes I and II were frequently isolated in humans (Kim and Weiss, 2018). Toxoplasmosis was estimated to infect about one-third of people globally (Montoya and Liesenfeld, 2004). Latin America, Eastern and Central Europe, Middle East, South-East Asia, and Africa are regions recorded to be with a high prevalence (Fuglewicz *et al*, 2017). Seroprevalence of *T. gondii* infection varied across those countries and was correlated with various sociodemographic and risk factors, including pregnancy, age, ethnicity, residence, water supply, and pets (Alvarado-Esquivel *et al*, 2011; Cong *et al*, 2015; Muflikhah *et al*, 2018; Achaw *et al*, 2019; Tamam and Alhusseiny, 2020). Acute *Toxoplasma* infection was indicated by a low avidity IgG, but a high IgG avidity indicated a longer-than-three-month-old chronic one (Berredjem *et al*, 2017; Chemoh *et al*, 2019).

Toxoplasma gondii infection was found to play a significant role in the pathogenesis of numerous psychiatric disorders, including patients unable to interpret details that typically corresponded with cognitive ability and depressive illness, such as mental retardation and schizophrenia (Del Grande *et al*, 2017; Muflikhah *et al*, 2018; Helaly and Ghorab, 2023). In Poland in 1953, first research on association between *T. gondii* infect-

ion and psychiatric patients was published (Kozar, 1953).

Many studies linked between toxoplasmosis exposure and schizophrenia, bipolar disorder, and major depressive disorder (MDD), and found a significant association, but not with MDD (Sutterland *et al*, 2015; Fernandes *et al*, 2021). Others linked *T. gondii* seropositivity to symptoms of depression and anxiety (Groër *et al*, 2011; Duffy *et al*, 2015), generalized anxiety disorder (Markovitz *et al*, 2015), obsessive-compulsive disorder (Miman *et al*, 2010), suicidality (Zhang *et al*, 2012), mixed anxiety and depressive disorder (Alvarado-Esquivel *et al*, 2016) and aggression and impulsivity (Cook *et al*, 2015). But, contradictory findings were reported (Gale *et al*, 2014; Sudgen *et al*, 2016). Nessim *et al*. (2023) in their meta-analysis study conducted for the year 2019 stated that the population fraction attributable of mental disease associated with toxoplasmosis was 20.4% for schizophrenia; 27.3% for bipolar disorder; and 0.29% for suicidal behavior. Toxoplasmosis had been extensively studied as a risk factor for neuropsychiatric disorders. Possible mechanisms included immunopathology and blood-brain barrier disruption (Xiao *et al*, 2018; Helaly and Ghorab, 2023).

The psychiatric disorder for which *T. gondii* investigated extensively is schizophrenia, and a substantial body of research showed that people with schizophrenia had significantly higher serum levels of *T. gondii* antibodies (Sutterland *et al*, 2015; de Barros *et al*, 2017; Morsy *et al*, 2021).

Toxoplasmosis was debatable as a risk factor for bipolar disorder. While some studies linked between *T. gondii* seropositivity and bipolar disorder, others refuted the idea that *T. gondii* infection could serve as a potential risk factor for the condition (Del Grande *et al*, 2020; Ýnceboz and Inceboz, 2021).

The role of *T. gondii* in the development of psychiatric illnesses was shown to be both directly, by affecting neurons, glial cells, and brain structures, and indirectly, by inducing a specific immune response and the

subsequent release of proinflammatory cytokines & neurotoxic factors (Yüksel and Kocazeybek, 2013; Del Grande *et al.*, 2017). In the toxoplasmosis latent stage, the parasite could persist within cysts in the host's muscle cells, astrocytes, microglia, and neurons throughout life (Halonen and Weiss, 2013).

Toxoplasma gondii infection in mice was found to increase the level of dopamine in the brain (Henriquez *et al.*, 2009). This finding was supported by the observation of an increase in dopamine release in neuronal cultures containing parasite cysts (Prandovszky *et al.*, 2011). Also, chronic toxoplasmosis was linked to higher extracellular glutamate concentrations and lower levels of glutamate transporter GLT-1 in astrocytes (David *et al.*, 2016). Increased levels of glutamate (Chang *et al.*, 2007) and decreased hippocampal volume (Kraguljac *et al.*, 2013) were in schizophrenic patients. According to Fuglewicz *et al.* (2017) schizophrenia was linked to changes in levels of many neurotransmitters, such as dopamine, glutamate, serotonin, and gamma amino butyric acid (GABA), as well as increased kynurenic acid (KYNA) in cerebrospinal fluid (Erhardt *et al.*, 2001), CNS (Plitman *et al.*, 2017) and serum (Morsy *et al.*, 2021). It was suggested that abnormal KYNA accumulation causes N-methyl-D-aspartate receptor (NMDA-R) hypo-function in schizophrenic patients (Zádor *et al.*, 2019).

Inhibiting KYNA formation thereby, improved neurotransmitter signaling and cognitive impairments (Zádor *et al.*, 2019). It was noted that mice with chronic *T. gondii* infection got higher amounts of KYNA, 3-Hydroxykynurenine (3-HK), and quinolinic acid (QUIN) in their brains (Notarangelo *et al.*, 2014). Treatment with anti-parasitic drugs allowed levels of these metabolites to return to normal, revealing the direct link between brain infection and activation of kynurenine pathway (KP) (Notarangelo *et al.*, 2014).

In latent toxoplasmosis, the development of low-grade chronic neuroinflammation defined by the up-regulation of proinflammatory cytokines such as tumor necrosis factor,

interleukin-12, interleukin-1 β and interferon-gamma (IFN γ) were thought to be the trigger for the activation of the KP (Tedford and McConkey, 2017). Also, KP activation was reported to cause a downstream release of the neuroactive substances KYNA and QUIN, which have an impact on neuronal functions (Braidy and Grant, 2017).

A reported mechanism of *T. gondii* in the onset of depression was that host immune response activated to produce proinflammatory cytokines (IL-6 & TNF). Depression was found to result from a decrease in serotonin synthesis in the brain (Webster and McConkey, 2010; Dalimi and Abdoli, 2012). A study found that two *T. gondii* genes encode tyrosine and phenylalanine hydroxylases that catalyzed the conversion of phenylalanine to tyrosine. Tyrosine was converted into dopa, the first step in the production of dopamine that specifically modifies behavior (Gaskell *et al.*, 2009; Henriquez *et al.*, 2009). To understand the relation between *T. gondii* and dysthymia or mild to moderate depression, more research was required as stated in literature (Saadatnia and Golkar, 2012; Sutherland *et al.*, 2015). Nessim *et al.* (2023) reported that, toxoplasmosis and mental health should be a research priority given the enormous potential impact of reducing this parasite in general population.

2- Malaria: According to the World Malaria Report, there were 241 million malaria cases in 2020 as opposed to 227 million cases in 2019 (WHO, 2022a). Malaria is a disease caused by *Plasmodium* spp. even with adequate antimalarial treatment that in cerebral form could cause vascular blockage, decreased cerebral blood flow, and other alterations that might result in acute or long-term neurological deficits (Monterio *et al.*, 2014). Cerebral malaria (CM), with impaired consciousness, prostration, multiple convulsions, deep breathing and respiratory distress (metabolic acidosis), acute pulmonary edema and acute respiratory distress syndrome, circulatory collapse or shock, and acute kidney injury were in clinical features of *P. falciparum*

severe malaria (Idro *et al*, 2005; 2010a).

Two patterns of neuropsychological sequelae were found to be associated with CM, depending on the time of symptoms onset (Idro *et al*, 2010a). The first was immediate and was characterized by status epilepticus and coma during the acute illness, leading to focal sequelae such as hemiplegia and focal seizures, or multifocal sequelae with spastic quadriparesis, motor abnormalities, cognitive and behavioral impairment, blindness, speech, or hearing impairment. Within months or years following CM, the second pattern (post-malaria neurological syndrome) were found to appear, and behavioral impairments and/or epilepsy would be present. Clinically, this picture showed as confusion, a slight stupor, or even psychosis. However, it was noticed to quickly worsen to the point of seizures and coma with a decerebrate posture (Mufaddel *et al*, 2014).

Sometimes, the first sign of cerebral involvement during malaria infection was found to be overtly psychotic behavior. Hallucinations, delusions, mania, and paranoid psychosis were the most prevalent neuropsychiatric complications in some cases (Kumar *et al*, 2003). Long-term cognitive impairment, acquired language problem, inattention, impulsiveness and hyperactivity, conduct disorders, obsessive symptoms, and impaired social development were found to happen among the neuropsychiatric impairments caused by CM in children. Also, destructive and injurious behaviors were noted (Markham and Koenig, 2011).

Post-malaria neurological syndrome was noticed to develop after symptomatic malarial infection and clearance of parasites from blood. It was found to be characterized by the emergence of neurological and psychiatric symptoms, which could happen one to four months after exposure. Generalized convulsion, delayed cerebellar ataxia, inappropriate speech or behavior, aggression, psychosis with auditory or visual hallucinations, catatonia with waxy flexibility, fine postural tremor, and reduced muscle tone were the

clinical manifestations (Kumar *et al*, 2003). Attention deficit hyperactivity disorder (ADHD), which causes deficits in the cognitive, behavioral, and interpersonal domains, hyper-activity, impulsiveness, and inattentiveness had also been seen in CM survivors (Idro *et al*, 2010b; Nevin and Croft, 2016). Mostly, damage caused by CM in the frontostriatal and cerebellar areas by a reduction in local blood flow or neuronal loss produced impairments in dopamine signaling and consequently ADHD (Lou *et al*, 1989).

There were postulated pathological mechanisms that cause neurological complications and mortality in cerebral malaria. Infected erythrocytes, platelets, and activated leukocytes were thought to trigger inflammatory events because of elevated adhesion molecules on the inflamed endothelium, which could reduce microvascular blood flow and could decrease the delivery of nutrients to the affected brain tissue and vessel walls, followed by bleeding and neuronal alternations (Newton *et al*, 1998; Faille *et al*, 2009; Cox and Mc Conkey, 2010; Monterio *et al*, 2014). Another mechanism related to common mental and psychotic symptoms associating CM was found to be immune mediated via increased level of TNF- α (Jenkins *et al*, 2019).

An important part of pathogenesis of CM was found to be played by disturbances in the homeostasis of cerebral microcirculation, which resulted in vascular obstructions, decreased cerebral blood flow, and blood-brain barrier disruption associated with high cerebral vasoconstriction, which in the presence of seizures and/or fever could cause increases metabolic demands with a consequent risk of neural injury (Kennan *et al*, 2005; Abbott *et al*, 2006; Idro *et al*, 2006; Monterio *et al*, 2014).

Almost all anti-malarial medications, with the exception of artemisinin derivatives, were found to be associated with neuropsychiatric symptoms (Grabias and Kumar, 2016). Neuropsychiatric side effects from mefloquine treatment developed in roughly

28% of *P. falciparum* malaria patients (Ronn *et al*, 1998). While artemisinin or antifolates were not known to be linked to neuropsychiatric complications, all quinoline antimalarial medications were known for their neuropsychiatric side effects (Telgt *et al*, 2005). Mefloquine's neuropsychiatric side effects included anxiety, paranoia, depression, hallucinations, psychotic behavior, and even suicidal thoughts. A prodromal stage of moderate symptoms such as dizziness, insomnia, and generalized anxiety as stated could precede mefloquine-induced psychosis, which could progress to a full-blown psychosis with paranoid delusions and psychomotor agitation (Tran *et al*, 2006; Nevin and Croft, 2016). Neuropsychiatric symptoms such as increased psychomotor activity, disorientation, excessive talking, delirium, confusion, increased need for sleep or insomnia, auditory hallucinations, and mania-like symptoms were linked to chloroquine treatment (Garg *et al*, 1990; Aneja *et al*, 2019; Talarico *et al*, 2022).

3a: Human African Trypanosomiasis: Human African trypanosomiasis (HAT), also known as African sleeping sickness, is a vector-borne parasitic disease. African trypanosomiasis, which is caused by parasites of the genus *Trypanosoma* and spread by infected tsetse flies, was found to be endemic in 36 sub-Saharan African Nations. More than 95% of cases documented were due to *Trypanosoma brucei gambiense* (WHO, 2022 b).

The clinical presentation of HAT was divided into two distinct phases: The early haemolymphatic stage and the late encephalitic stage, which could affect the central nervous system. Within a few months after initial infection by *rhodesiense* type, the disease could start acutely (the parasite invades the CNS early), but it could also start slowly, with chronic symptoms and a late CNS infection lasting months to years as with the *gambiense* type (Morys *et al*, 2015). The initial manifestation of the disease was noticed to be insidious in the late (encephalitic) stage, and the range of potential clinical

phenotypes was broad (Atouguia and Kennedy, 2000). Due to the wide range of reported neurologic symptoms, they were grouped into broad categories such as psychiatric, motor, and sensory abnormalities, and sleep disorders. Mental disturbances might be subtle and included irritability, lassitude, headache, obvious personality changes, and psychiatric presentations like violence, hallucinations, suicidal tendencies, and mania (Atouguia and Kennedy, 2000; Kone' *et al*, 2021). Typical sleep disturbances included lethargy, distractibility, and uncontrollable urges to sleep, as well as a reversal of typical sleep-wake cycle in which nocturnal insomnia alternated with daytime somnolence. Reactivated disease with CNS involvement could develop in leukemia, lymphoma, Hodgkin's disease, transplantation, and AIDS patients (Kennedy, 2004).

Meningoencephalitis, with cellular proliferation in the leptomeninges and a diffuse perivascular white matter infiltration dominated by lymphocytes, plasma cells, and macrophages, were found to be the pathologic basis of late-stage sleeping sickness. Markedly active macrophages and astrocytes were found in the perivascular cuffs and adjacent parenchyma, and pathognomonic morula or Mott cells that were assumed to be modified plasma cells with eosinophilic inclusions comprising IgM, could be found in white matter (Adams *et al*, 1986; Atouguia and Kennedy, 2000).

Patients with CNS sleeping sickness were found to have altered cytokine levels. For instance, significant elevations of IL-10 were seen in the plasma and CSF in both early and late stages of *rhodesiense* illness, and they decreased after therapy to levels seen in control subjects, who were not infected (MacLean *et al*, 2001).

In late-stage disease compared to levels found following treatment, total but not free plasma TNF-levels were also increased. However, uncertainty surrounded the source of the elevated IL-10. Similar studies in *gambiense*-infected patients have also noted

elevated CSF IL-10 levels in late-stage illness, along with a rise in IL-6 and IL-8 levels (Lejon *et al*, 2002).

Other alterations which were noted in patients with CNS HAT included very high CSF prostaglandin D2 levels (Pentreath, 1995), which was related to the marked somnolence, and elevated blood and CSF endotoxin levels corresponded to the CNS pathology (Pentreath, 1989). Therefore, early astrocyte activation was probably crucial in triggering the inflammatory response in the central nervous system. Also, during trypanosomiasis, the monoaminergic neurotransmitters dopamine, serotonin, and norepinephrine were altered in brain, which could be a factor in the neuropsychiatric disorders seen in HAT (Stibbs and Curtis, 1987; Amole *et al*, 1989).

A study showed that biomarkers in CSF were able to distinguish patients at 1st stage or advanced 2nd stage of HAT with absolute specificity. Two of these biomarkers; neopterin and 5-hydroxytryptophan showed 100% specificity and sensitivity between the two stages of the disease in patients' samples. Neopterin was found to be an inflammatory biomarker previously shown in CSF of 2nd stage but not 1st stage patients. 5-hydroxytryptophan was recorded to be an important metabolite in the serotonin synthetic pathway, the key pathway in determining somnolence, thus offering a possible link to the eponymous symptoms of sleeping sickness. Following trypanosome invasion of the CNS, including an increase in 5-hydroxytryptophan, and a decrease in tryptophan in advanced 2nd stage of HAT patients was recorded. This change was accompanied by a small increase in kynurenine in advanced stage disease (Vincent *et al*, 2016)

3b: American Trypanosomiasis (Chagas disease): Chagas disease (CD), also known as American trypanosomiasis, is a potentially fatal disease caused by the protozoan parasite *Trypanosoma cruzi*. It was found to affect 6 to 7 million people worldwide. Chagas disease was mostly found in endemic

regions of 21 countries in continental Latin America, where it was mostly spread when people come into contact with the feces of infected blood-sucking triatomine bugs i.e., vector-borne transmission (WHO, 2018).

Trypanosoma cruzi infection was found to yield inflammation mainly in the heart and gastrointestinal tract. Since the parasite were also found to prefer brain cells including microglia, astrocytes, and neurons (Corrêa-De-Santana *et al*, 2006), it could influence the nervous system (Da Silva *et al*, 2010). The disease has an acute and a chronic phase. One-third of patients could progress to the chronic stage of the illness. Chronic CD were found to typically begins with a latency period known as chronic indeterminate form, which could go undiscovered for more than 30 years or the entirety of one's life. The majority of those who have been infected were noticed to continue to be so. However, this indeterminate form might occasionally be followed by symptomatic forms of the chronic phase, which noted to be characterized by a decline in parasitemia and by cardiac, digestive, or neurological manifestations (Prata, 2001; Clayton, 2010; Lidani *et al*, 2019). Besides, the behavioral changes and development of psychiatric comorbidities like anxiety and depression could occur during the chronic phase of CD, conditions that, in principle, could not be solely attributed to patient's psychological state (Jackson *et al*, 2012; Vilar-Pereira *et al*, 2015; Suman *et al*, 2017).

The understanding of the major depressive disorder could be attributed to an immune-inflammatory condition, where activated neuro-immune and related oxidative pathways caused alterations in brain neurons resulting in symptoms of depression (Maes, 1995; Wichers *et al*, 2005). This psychiatric condition was found to make CD worse and make the patients feel even more heavily burdened, substantially impairing their life quality (Ozaki *et al*, 2011; Duarte-Silva *et al*, 2020).

4- Neurocysticercosis: A well-known neuroparasitosis in humans especially in pork

consuming countries is neurocysticercosis (NCC), a parasitic infection of CNS (Daré *et al*, 2019). The clinical signs and symptoms of NCC were found to vary and rely on the topography, number, size, and stage of lesions, in addition to the immunological response of the host to the parasite (Del Brutto *et al*, 2001).

The initial immune response to *cysticerci* was recorded to be minimal, which could explain the long latent period. Seizures, headache, intracranial hypertension caused by an obstruction in cerebrospinal fluid (CSF) flow, stroke, ophthalmologic, and endocrinological manifestations were found to be among the commonest NCC symptoms and signs (Garcia and Del Brutto, 2005).

Seizure were recorded to be the most frequent clinical manifestation of intraparenchymal NCC, whereas in extraparenchymal NCC, which referred to infections of ventricles and subarachnoid spaces; manifestations included hydrocephalus, dysfunction of multiple cranial nerves, visual and hormonal impairment attributed to compression of the hypophyseal stem and optic nerves (Arriada-Mendicoa *et al*, 2003; Sinha and Sharma, 2009).

The severity of psychiatric symptoms was correlated with the use of anti-parasitic medications to treat NCC, associated with an increase in CNS inflammation (Fortenza *et al*, 1997). Confusion, disorientation, memory loss, hallucinations, psychomotor incoordination, progressive worsening of language ability and mental deterioration were the most reported mental alterations (Verma *et al*, 2011).

While cognitive decline was in 87.5% of NCC patients, psychiatric disorders were in 66.8% of people. Depressive disorders and psychosis were found in 52.6% and 14.2% of cases, respectively (Fortenza *et al*, 1997; Daré *et al*, 2019). Schizophrenic and manic-like episodes were reported as potential early NCC signs in another study by Moryś *et al*. (2015), who also proposed that psychiatric symptoms of NCC were not caused by

the parasite's direct impact on specific brain tissue, but rather related to mechanical changes in CSF pressure and inflammatory damage to the brain parenchyma.

About one-fifth of NCC patients were recorded with dementia, which could be an important presenting symptom (Biswas *et al*, 1998; Wiwanitkit, 2014). In contrast to degenerative dementia, which primarily affects the elderly, dementias associated with NCC were found to occur in people of any age. Seizures and hallucinations were recorded to be two neuropsychiatric manifestations that could occasionally co-exist with dementia (Shah and Chakrabarti, 2013).

Dementia syndrome seen in individuals with NCC were found to result from a combined effect of multiple parasitic and vascular lesions, disrupting fronto-parieto-temporal networks related to intellectual performance in patients with susceptible brains (due to recurrent epileptic seizures, a lack of education, and advanced age) (Ramirez-Bermudez *et al*, 2005).

5: Human toxocariasis: Human toxocariasis is a zoonotic and worldwide distributed disease due to infection by the larval stages of *Toxocara canis* and *T. cati*, the common roundworms of canids or felids, respectively (Ma *et al*, 2018; Eslahi *et al*, 2020). Almost 1.4 billion people world-wide were reported exposed to or infected with *Toxocara* species (Rostami *et al*, 2019). Human infection resulted through ingesting *Toxocara* eggs from contaminated vegetables, food, or soil, as well as from larvae in undercooked or raw meats from paratenic hosts like cows, sheep or chickens (Fakhri *et al*, 2018; Rostami *et al*, 2020a;b). Juvenile larvae in the paratenic hosts, were found to migrate to various organs via systemic circulation, but did not grow into mature worms (Ma *et al*, 2018).

Clinical syndromes brought on by larvae migration included common/covert toxocariasis; ocular larva migrans, and visceral larva migrans (Taylor and Holland, 2001). Furthermore, *Toxocara spp.* by breaching the

blood-brain barrier and invading the CNS, larvae were found to cause neurotoxocariasis (NT) (Deshayes *et al*, 2016). Local or generalized inflammation was brought on during larvae migration, mainly as a result of eosinophilia or increased production of pro-inflammatory cytokines and particular antibodies (Ma *et al*, 2018). The main clinical complications of NT included encephalitis, meningitis, myelitis, cerebral vasculitis, multiple sclerosis, epilepsy, and behavior disorders (Söndergaard and Theorell, 2004; Quattrocchi *et al*, 2012; Alvarado-Esquivel, 2013).

Toxocara spp. was suggested as a possible etiology of schizophrenia (Kaplan *et al*, 2008; Khademvatan *et al*, 2014; Taghipoura *et al*, 2021). Through its interaction with different neurobiological pathways, inflammation was found to play a role in the pathophysiology of several neuropsychiatric illnesses (Khandaker *et al*, 2015). Multiple stimulating factors, such as infectious agents, could induce inflammation (Johnson and Foster, 2018; Taghipour *et al*, 2019; 2022). As a result, *Toxocara* infection was recorded to serve as an amplifier of inflammation that consequently involved in aetiopathogenesis of schizophrenia (Taghipour *et al*, 2021).

Conclusions

Neurotropic parasitic infections were recorded to be frequently associated with neuropsychiatric disorders. Additionally, drugs that are commonly prescribed to treat tropical illnesses like in case of antimalarial drugs were found to affect mood and result in psychosis. Neurological and psychiatric impairments induced by these types of parasitic infections, which reported to cause profound changes in the nervous system functions, frequently associated with severe sequels or late-onset disturbances. It is therefore crucial to spread information about the neuropsychiatric symptoms that could be present in conjunction with neurotropic parasitic infections to raise awareness of these problems and challenges. Prevention and control of these parasitic CNS infections, therefore, remains a global research priority.

Authors' declaration: The authors declared that they have neither competing interests nor received any funds.

Authors reported that they equally share in this article review

References

- Abbott, NJ, Ronnback, L, Hansson, E, 2006:** Astrocyte-endothelial interactions at the blood-brain barrier. *Nat. Rev. Neurosci.* 7:41.
- Achaw, B, Tesfa, H, Zeleke, AJ, Worku, L, Addisu, A, et al, 2019:** Sero-prevalence of *Toxoplasma gondii* and associated risk factors among psychiatric outpatients attending University of Gondar Hospital, Northwest Ethiopia. *BMC Infect. Dis.* 19:581.
- Adams, JH, Haller, L, Boa, FY, Doua, F, Dago, A, Konian, K, 1986:** Human African trypanosomiasis (*T.b. gambiense*): A study of 16 fatal cases of sleeping sickness with some observations on acute reactive arsenical encephalopathy. *Neuropathol. Appl. Neurobiol.* 12:81.
- Alvarado-Esquivel, C, 2013:** *Toxocara* infection in psychiatric inpatients: A case control seroprevalence study. *PLoS One* 8, 4:e62606.
- Alvarado-Esquivel, C, Urbina-Álvarez, JD, Estrada-Martínez, S, Torres-Castorena, A, Molotla-De-León, G, et al, 2011:** *Toxoplasma gondii* infection and schizophrenia: A case-control study in a low *Toxoplasma* seroprevalence Mexican population. *Parasitol. Int.* 60:151.
- Alvarado-Esquivel, C, Sanchez-Anguiano, L F, Hernandez-Tinoco, J, Berumen-Segovia, L O, Torres-Prieto, YE, et al, 2016:** *Toxoplasma gondii* infection and mixed anxiety and depressive disorder: a case-control seroprevalence study in Durango, Mexico. *J. Clin. Med. Res.* 8:519.
- Amole, B, Sharpless, N, Wittner, M, Tanowitz, HB, 1989:** Neurochemical measurements in the brains of mice infected with *Trypanosoma brucei*. *Ann. Trop. Med. Parasitol.* 83, 3: 225.
- Aneja, J, Goya, D, Choudhary, B, 2019:** Psychosis consequent to antimalarial drug use in a young child. *J. Fam. Med. Prim. Care* 8, 5:1781.
- Arriada-Mendicoa, N, Celis-Lopez, MA, Higuera-Calleja, J, 2003:** Imaging features of sellar cysticercosis. *Am. J. Neuroradiol.* 24:1389.
- Atouguia, JLM, Kennedy, PGE, 2000:** Neurological aspects of human African trypanosomiasis. In: Davis, LE, Kennedy, PGE, eds. *Infectious diseases of the nervous system*. Butterworth-Heinemann, Oxford.
- Berredjem, H, Aouras, H, Benlaifa, M, Beche-**

- ker, I, Djebbar, MR, 2017:** Contribution of IgG avidity and PCR for the early diagnosis of toxoplasmosis in pregnant women from the North-Eastern region of Algeria. *Afr. Hlth. Sci.* 17:647.
- Biswas, A, Prasad, A, Anand, KS, 1998:** Cysticercal dementia. *Ind. J. Asso. Physician* 46: 569.
- Braidy, N, Grant, R, 2017:** Kynurenine pathway metabolism and neuroinflammatory disease. *Neural. Regen. Res.* 12:39.
- Burgdorf, K.S., Trabjerg, B.B, Pedersen, M G, 2019:** Large-scale study of *Toxoplasma* and Cytomegalovirus shows an association between infection and serious psychiatric disorders. *Brain Behav. Immun.* 79:152.
- Chang, L, Friedman, J, Ernst, T, Zhong, K, Tsopelas, ND et al, 2007:** Brain metabolite abnormalities in the white matter of elderly schizophrenic subjects: implication for glial dysfunction. *Biol. Psychiat.* 62:1396.
- Chemoh, W, Nur, FMN, Noor, AMA, Si, LK, Sawangjaroen, N, et al, 2019:** Prevalence and risk factors of *Toxoplasma* infection: An update in Malaysian pregnant women. *Trop. Biomed.* 36:694.
- Chen, X, Chen, B, Hou X, Zheng C, Yang X, 2019:** Association between *Toxoplasma gondii* infection & psychiatric disorders in Zhejiang, Southeastern China. *Acta. Trop.* 192:82.
- Clayton, J, 2010:** Chagas disease. *Nature* 465: S4.
- Cong, W, Dong, W, Bai, L, Wang, XY, Ni, X T, et al, 2015:** Seroprevalence and associated risk factors of *Toxoplasma gondii* infection in psychiatric patients: A case-control study in eastern China. *Epidemiol. Infect.* 143:3103.
- Cook, TB, Brenner, LA, Cloninger, CR, Langenberg, P, Igbide, A, et al, 2015:** “Latent” infection with *Toxoplasma gondii*: Association with trait aggression and impulsivity in healthy adults. *J. Psychiatr. Res.* 60:87.
- Corrêa-De-Santana, E, Pinto-Mariz, F, Savino, W, 2006:** Immunoneuroendocrine interactions in Chagas disease. *Ann. N. Y. Acad. Sci.* 1088:274.
- Cox, D, Mc Conkey, S, 2010:** The role of platelets in the pathogenesis of cerebral malaria. *Cell. Mol. Life Sci.* 67:557
- Dalimi, A, Abdoli, A, 2012:** Latent toxoplasmosis and human. *Iran. J. Parasitol.* 7:1.
- Daré, LO, Bruand, PE, Gérard, D, Marin, B, Lameyre, V, 2019:** Associations of mental disorders and neurotropic parasitic diseases: A meta-analysis in developing and emerging countries. *BMC. Publ. Hlth.* 19, 1:1645.
- Da Silva, AA, Pereira, GV, de Souza AS, Silva, RR, Rocha, MS et al, 2010:** *Trypanosoma cruzi*-induced central nervous system alterations: From the entry of inflammatory cells to potential cognitive and psychiatric abnormalities. *J. Neuroparasitol.* 1:1.
- David, CN, Frias, ES, Szu, JI, Vieira, PA, Hubbard, JA, et al, 2016:** GLT-1-dependent disruption of CNS glutamate homeostasis and neuronal function by the protozoan parasite *Toxoplasma gondii*. *PLoS Pathog.* 12: e1005643.
- De Barros, VM, Barbosa, IG, Salem, H, Rocha, NP, Kummer, A. et al, 2017:** Is there any association between *Toxoplasma gondii* infection and bipolar disorder? A systematic review and meta-analysis. *J. Affect. Disord.* 209:59.
- Del Brutto, OH, Rajshekhar, V, White, AC, 2001:** Proposed diagnostic criteria for neurocysticercosis. *Neurol.* 57:177.
- Del Grande, C, Galli, L, Schiavi, E, Dell’osso, L, Bruschi, F, 2017:** Is *Toxoplasma gondii* a trigger of bipolar disorder? *Pathology* 6:3.
- Del Grande, C, Schiavi, E, Masci, I, Barbuti, M, Maccariello, G et al, 2020:** Toxoplasmosis in a cohort of Italian Patients with bipolar and psychotic disorders: How infection may affect clinical features? *J. Nerv. Ment. Dis.* 208:118.
- Deshayes, S, Bonhomme, J, de La Blanchardière, A, 2016:** Neurotoxocariasis: A systematic literature review. *Infection* 44, 5:565.
- Duarte-Silva, E, Maes, M, Macedo, D, Wilson Savino, W, Peixoto, CA, 2020:** Shared neuro-immune and oxidative pathways underpinning Chagas disease and major depressive disorder. *Trans. Psychiat.* 10:419.
- Duffy, AR, Beckie TM, Brenner, LA, Beckstead, JW, Seyfang, A, et al, 2015:** Relationship between *Toxoplasma gondii* and mood disturbance in women veterans. *Mil. Med.* 180:621.
- Elsheikha, HM, Azab, MS, Abousamra, NK, Rahbar, MH, Elghannam, DM, et al, 2009:** Seroprevalence of and risk factors for *Toxoplasma gondii* antibodies among asymptomatic blood donors in Egypt. *Parasitol. Res.* 104:1471.
- Elsheikha, HM, Büsselberg, D, Zhu, XQ, 2016:** The known and missing links between *Toxoplasma gondii* and schizophrenia. *Metab. Brain Dis.* 31:749.
- Erhardt, S, Blennow, K, Nordin, C, Skogh, E, Lindström, LH, et al, 2001:** Kynurenic acid levels are elevated in the cerebrospinal fluid of pa-

- tients with schizophrenia. *Neurosci. Lett.* 313: 96.
- Eslahi, AV, Badri, M, Khorshidi, A, 2020:** Prevalence of *Toxocara* and *Toxascaris* infection among humans and animals in Iran with a meta-analysis approach. *BMC Infect. Dis.* 20, 1:1.
- Faille, D, El-Assaad, F, Alessi, MC, 2009:** Platelet-endothelial cell interactions in cerebral malaria: The end of a cordial understanding. *Thromb. Haemost.* 102:1093.
- Fakhri, Y, Gasser, R, Rostami, A, 2018:** *Toxocara* eggs in public places worldwide: A systematic review and meta-analysis. *Environ Pollut.* 242:1467.
- Fernandes, SM, Dias, AR, Miranda-Scippa, A, 2021:** Association between exposure to toxoplasmosis and major psychiatric disorders: A systematic review. *Braz. J. Psychiat.* 43, 4:438.
- Forlenza, OV, Filho, AH, Nobrega, JP, 1997:** Psychiatric manifestations of neurocysticercosis: A study of 38 patients from a neurology clinic in Brazil. *J. Neurol. Neurosurg. Psychiat.* 62: 612.
- Fuglewicz, AJ, Piotrowski, P, Stodolak, A, 2017:** Relationship between toxoplasmosis and schizophrenia: a review. *Adv. Clin. Exp. Med.* 26:1033.
- Gale, SD, Brown, BL, Berrett, A, Erickson, L D, Hedges, DW, 2014:** Association between latent toxoplasmosis and major depression, generalized anxiety disorder, and panic disorder in human adults. *Folia Parasitol. (Praha)* 61:285.
- Garcia, HH, Del Brutto, OH, 2005:** Neurocysticercosis: Updated concepts about an old disease. *Lancet Neurol.* 4:653.
- Garg, P, Mody, P, Lall, KB, 1990:** Toxic psychosis due to chloroquine: not uncommon in children. *Clin. Pediatr. (Phila)* 29:448.
- Gaskell, EA, Smith, JE, Pinney, JW, Westhead, DR, Mc-conkey, GA, 2009:** A unique dual activity amino acid hydroxylase in *Toxoplasma gondii*. *PLoS One* 4:e4801.
- Gazzinelli, RT, Kalantari, P, Fitzgerald, KA, Golenbock, DT, 2014:** Innate sensing of malaria parasites. *Nat. Rev. Immunol.* 14, 11: 744.
- Ghanem, M., Gadallah, M, Meky, F, Mourad, S, El-Kholy, G, 2009:** National survey of prevalence of mental disorders in Egypt: A preliminary survey. *East. Mediterr. Hlth. J.* 15, 1:65.
- Grabias, B, Kumar, S, 2016:** Adverse neuropsychiatric effects of antimalarial drugs. *Exp. Opin. Drug Safety* 15:903.
- Groër, MW, Yolken, RH, Xiao, JC, Beckstead, JW, Fuchs, D, et al, 2011:** Prenatal depression and anxiety in *Toxoplasma gondii*-positive women. *Am. J. Obstet. Gynecol.* 204:433.
- Halonen, SK, Weiss, LM, 2013:** Toxoplasmosis. *Handb. Clin. Neurol.* 114:125.
- Helaly, AMN, Ghorab, DS, 2023:** Schizophrenia as metabolic disease. What are the causes? *Met. Br. Dis.* <https://doi.org/10.1007/s11011022-01147-6>
- Henriquez, SA, Brett, R, Alexander, J, Pratt, J, Roberts, CW, 2009:** Neuropsychiatric disease and *Toxoplasma gondii* infection. *Neuroimmunomod.* 16:122.
- Idro, R, Jenkins, NE, Newton, C, 2005:** Pathogenesis, clinical features, and neurological outcome of cerebral malaria. *Lancet Neurol.* 4:827.
- Idro, R, Carter, JA, Fegan, G, 2006:** Risk factors for persisting neurological and cognitive impairments following cerebral malaria. *Arch. Dis. Child.* 91:142.
- Idro, R, Kakooza-Mwesige, A, Balyejjussa, S, 2010a:** Severe neurological sequelae and behavior problems after cerebral malaria in Ugandan children. *BMC Res. Notes* 3:104.
- Idro, R, Marsh K, John, CC, 2010b:** Cerebral malaria: Mechanisms of brain injury and strategies for improved neurocognitive outcome. *Pediatr. Res.* 68:267.
- Idro, R, Ogwang, R, Barragan, A, Raimondo, JV, Masocha, W, 2022:** Neuroimmunology of common parasitic infections in Africa. *Front. Immunol.* 10, 13:791488.
- Jackson, Y, Castillo, S, Hammond, P, Besson, M, Brawand-Bron, A, et al, 2012:** Metabolic, mental health, behavioral and socioeconomic characteristics of migrants with Chagas disease in a non-endemic country. *Trop. Med. Int. Hlth.* 17: 595.
- Jenkins, R, Ong'echa, M, Othieno, C, Ongeri, L, Sifuna, P, et al, 2019:** Malaria, mental disorders, immunity and their interrelationships: A cross sectional study in a household population in a health and demographic surveillance site in Kenya. *E. Bio. Med.* 39:369.
- Johnson, KV-A, Foster, KR, 2018:** Why does the microbiome affect behavior? *Nat. Rev. Microbiol.* 16, 10:647.
- Kaplan, M, Kalkan, A, Kuk, S, 2008:** *Toxocara* seroprevalence in schizophrenic patients in Turkey. *Yonsei Med. J.* 49, 2:224.
- Kennan, RP, Machado, FS, Lee, SC, 2005:** Reduced cerebral blood flow and N-acetyl aspartate in a murine model of cerebral malaria. Para-

sitol. Res. 96:302.

Kennedy, PG (2004): Human African trypanosomiasis of the CNS: Current issues and challenges. *J. Clin. Invest.* 113:496

Khademvatan, S, Khajeddin, N, Izadi, S, 2014: Investigation of anti-*Toxocara* and anti-*Toxoplasma* antibodies in patients with schizophrenia disorder. *Schizophr. Res. Treat.* <http://dx.doi.org/10.1155/2014/230349>

Khandaker, GM, Cousins, L, Deakin, J, 2015: Inflammation and immunity in schizophrenia: implications for pathophysiology and treatment. *Lancet Psychiat.* 2, 3:258.

Kim, JJ, 2007: Viral infections as etiological factors of schizophrenia. *Psychiat. Investig.* 4:61.

Kim, K, Weiss, LM, 2018: The next 100 years. *Microb. Infect.* 97:1413.

Koné, M, Kaba, D, Kaboré, J, Thomas, L, Falzon, LC, 2021: Passive surveillance of human African trypanosomiasis in Côte d'Ivoire: Understanding prevalence, clinical symptoms and signs, and diagnostic test characteristics. *PloS Neglect. Trop. Dis.*; 15, 8: e0009656. <https://doi.org/10.1371/journal.pntd.0009656>.

Kozar, Z, 1953: Research on toxoplasmosis among the mentally ill. *Bull. Inst. Mar. Trop. Med. Gdansk.* 5:146. (In Polish)

Kraguljac, NV, White, DM, Reid, MA, Lahti, AC, 2013: Increased hippocampal glutamate and volumetric deficits in unmedicated patients with schizophrenia. *JAMA Psychiat.* 70:1294.

Kumar, D, Patel, N, Pradeep, P, 2003: Clinical manifestations of complicated malaria: An overview. *JACM* 4:323.

Lejon, V, Lardon, J, Kenis, G, Pinoges, L, Legros, D, et al, 2002: Interleukin (IL)-6, IL-8 and IL-10 in serum and CSF of *Trypanosoma brucei gambiense* sleeping sickness patients before and after treatment. *Trans. R. Soc. Trop. Med. Hyg.* 96:329.

Lidani, KCF, Andrade, FA, Bavia, L, 2019: Chagas disease: From discovery to a worldwide health problem. *Front. Publ. Hlth.* 7:166.

Lou, HC, Henriksen, L, Bruhn, P, 1989: Striatal dysfunction in attention deficit and hyperkinetic disorder. *Arch. Neurol.* 46:8.

Ma, G, Holland, CV, Wang, T, 2018: Human toxocariasis. *Lancet Infect. Dis.* 18, 1:e14.

Mac Lean, L, Odiit, M, Sternberg, JM, 2001: Nitric oxide and cytokine synthesis in human African trypanosomiasis. *J. Infect. Dis.* 184: 1086.

Maes, M, 1995: Evidence for an immune respo-

nse in major depression: a review and hypothesis. *Prog. Neuropsychopharmacol. Biol. Psychiat.* 19:11.

Maizels, RM, Smits, HH, Mc-Sorley, HJ, 2018: Modulation of host immunity by helminths: The expanding repertoire of parasite effector molecules. *Immunol.* 49, 5:801.

Mallewa, M, Wilmshurst, JM, 2014: Overview of the effect and epidemiology of parasitic central nervous system infections in African children. *Semin. Pediatr. Neurol.* 21, 1:19.

Markham, JA, Koenig, JI, 2011: Prenatal stress: Role in psychotic and depressive diseases. *Psychopharmacol. (Berl.)* 214:89.

Markovitz, AA, Simanek, AM, Yolken, RH, Galea, S, Koenen, KC, et al, 2015: *Toxoplasma gondii* and anxiety disorders in a community-based sample. *Brain Behav. Immun.* 43:192.

Miman, O, Mutlu, EA, Ozcan, O, Atambay, M, Karlidag, R, et al, 2010: Is there any role of *Toxoplasma gondii* in the etiology of obsessive-compulsive disorder? *Psychiat. Res.* 177:263.

Mohamed, Z, Hajissa, K, 2016: Seroprevalence of *Toxoplasma gondii* infection among patients in hospital Universiti Sains Malaysia. *Trop. Biomed.* 33:78.

Monteiro, MC, Oliveira, FR, Oliveira, GB, 2014: Neurological and behavioral manifestations of cerebral malaria: an update. *World J. Transl. Med.* 3:9.

Montoya, J, Liesenfeld, O, 2004: Toxoplasmosis. *Lancet* 363:1965.

Morsy, SM, Ismail, MA, Ghallab, MM, 2021: Seroprevalence of *Toxoplasma gondii* in schizophrenic patients versus healthy individuals and its possible impact on human serum dopamine level. *J. Egypt. Soc. Parasitol.* 51, 2: 365

Moryś, JM, Jeżewska, M, Korzeniewski, K, 2015: Neuropsychiatric manifestations of some tropical diseases. *Int. Marit. Hlth.* 66, 1: 30.

Mufaddel, A, Omer, AA, Omar, SM, 2014: Psychiatric aspects of infectious diseases. *Open J. Psychiatr.* 4:202.

Muflikhan, ND, Supargiyono, S, Artama, W T, 2018: Seroprevalence and risk factor of toxoplasmosis in schizophrenia patients referred to Grhasia Psychiatric Hospital, Yogyakarta, Indonesia. *Afr. J. Infect. Dis.* 12:76.

Nessim, PJ, Luna-Ramirez, JC, Moreno-Gómez, GA, Galvis-Soto, DM, Gomez-Marin, JE, 2023: Estimation of the number people with mental diseases associated with toxoplasmosis and identification of risk factors by continent.

- Psych. Res. (323): <https://doi.org/10.1016/j.psychres.2023.115130>.
- Nevin, LR, Croft, AM, 2016:** Psychiatric effects of malaria and anti-malarial drugs: Historical and modern perspectives. *Malar. J.* 15: 332.
- Newton, CR, Taylor, TE, Whitten, RO, 1998:** Pathophysiology of fatal falciparum malaria in African children. *Am. J. Trop. Med. Hyg.* 58: 673.
- Notarangelo, FM, Wilson, EH, Horning, KJ, Thomas, MR, Harris, TH, et al, 2014:** Evaluation of kynurenine pathway metabolism in *Toxoplasma gondii*-infected mice: Implications for schizophrenia. *Schizophr. Res.* 152:261.
- Ozaki, Y, Guariento, ME, De Almeida, EA, 2011:** Quality of life and depressive symptoms in Chagas disease patients. *Qual. Life Res.* 20: 133.
- Pentreath, VW, 1989:** Neurobiology of sleeping sickness. *Parasitol. Today* 5:215.
- Pentreath, VW, 1995:** Trypanosomiasis and the nervous system: Pathology and immunology. *Trans. R. Soc. Trop. Med. Hyg.* 89:9.
- Plitman, E, Iwata, Y, Caravaggio, F, Nakajima, S, Chung, JK, et al, 2017:** Kynurenic acid in schizophrenia: a systematic review and meta-analysis. *Schizophr. Bull.* 43:764.
- Prandovszky, E, Gaskell, E, Martin, H, Dubey, JP, Webster, JP, et al, 2011:** The neurotropic parasite *Toxoplasma gondii* increases dopamine metabolism. *PLoS One* 6:e23866.
- Prata, A, 2001:** Clinical and epidemiological aspects of Chagas disease. *Lancet Infect. Dis.* 1: 92.
- Quattrocchi, G, Nicoletti, A, Marin, B, 2012:** Toxocariasis and epilepsy: Systematic review and meta-analysis. *PLoS Negl. Trop. Dis.* 6, 8: e1775.
- Ramirez-Bermudez, J, Higuera, J, Sosa, AL, 2005:** Is dementia reversible in patients with neurocysticercosis? *J. Neurol. Neurosurg. Psychiatr.* 76:1164.
- Ronn, AM, Ronne-Rasmussen, J, Gotzsche, P C, 1998:** Neuropsychiatric manifestations after mefloquine therapy for *Plasmodium falciparum* malaria: Comparing a retrospective and a prospective study. *Trop. Med. Int. Hlth.* 3: 83.
- Rostami, A, Riahi, SM, Holland, C, 2019:** Seroprevalence estimates for toxocariasis in people worldwide: a systematic review and meta-analysis. *PLoS Negl. Trop. Dis.* 13, 12: e0007809.
- Rostami, A, Riahi, SM, Hofmann, AH, 2020a:** Global prevalence of *Toxocara* infection in dogs. *Adv. Parasitol.* 109: 561.
- Rostami, A, Sepidarkish, M, Ma, G, 2020b:** Global prevalence of *Toxocara* infection in cats. *Adv. Parasitol.* 109: 615.
- Saadatnia, G, Golkar, M, 2012:** A review on human toxoplasmosis. *Scand. J. Infect. Dis.* 44: 805.
- Shah, R, Chakrabarti, S, 2013:** Neuropsychiatric manifestations and treatment of disseminated neurocysticercosis: A compilation of three cases. *Asuan. J. Psychiatr.*; 6: 344.
- Sinha, S, Sharma, BS, 2009:** Neurocysticercosis: A review of current status and management. *J. Clin. Neurosci.* 16:867.
- Söndergaard, HP, Theorell, T, 2004:** A putative role for *Toxocara* species in the etiology of multiple sclerosis. *Med. Hypoth.* 63, 1:59.
- Stibbs, HH, Curtis DA, 1987:** Neurochemical changes in experimental African trypanosomiasis in voles and mice. *Ann. Trop. Med. Parasitol.* 81, 6:673.
- Sugden, K, Moffitt, TE, Pinto, L, Poulton, R, Williams, BS, et al, 2016:** Is *Toxoplasma gondii* infection related to brain and behavior impairments in humans? evidence from a population-representative birth cohort. *PLoS One* 11:e0148435.
- Suman, AC, da Costa, EN, Bazan, SZ, Hueb, JC, de Carvalho, FC, et al, 2017:** Evaluating respiratory musculature, quality of life, anxiety, and depression among patients with indeterminate chronic Chagas disease and symptoms of pulmonary hypertension. *Rev. Soc. Bras. Med. Trop.* 50: 194.
- Sutherland, AL, Fond, G, Kuin, A, Koeter, MW, Lutter, R, et al, 2015:** Beyond the association. *Toxoplasma gondii* in schizophrenia, bipolar disorder, and addiction: Systematic review and meta-analysis. *Acta Psychiatr. Scand.* 132: 161.
- Taghipour, A, Mosadegh, M, Kheirollahzadeh, F, 2019:** Are intestinal helminths playing a positive role in tuberculosis risk? A systematic review and meta-analysis. *PLoS One* 14, 10: e0223722.
- Taghipour, A, Habibpour, H, Mirzapour, A, Rostami, A, 2021:** *Toxocara* infection/exposure and the risk of schizophrenia: A systematic review and meta-analysis. *Trans. R. Soc. Trop. Med. Hyg.* 15, 10:1114.
- Taghipour, A, Bahadory, S, Badri, M, 2022:** A systematic review and metaanalysis on the coinfection of *Helicobacter pylori* with intestinal parasites: Public health issue or neglected correlation.

- ation? Int. J. Environ. Hlth Res. 32, 4: 808.
- Talarico, F, Chakravarty, S, Liu, YS, Greenshaw, AJ, Passos, IC, et al, 2022:** Systematic review of psychiatric adverse effects induced by chloroquine and hydroxychloroquine: Case reports and population studies. Ann. Pharmacother. Aug 4: Doi:10600280221113572.
- Taman, A, Alhusseiny, SM, 2020:** Exposure to toxoplasmosis among the Egyptian population: A systematic review. PUJ 13, 1:1.
- Taylor, MRH, Holland, CV, 2001:** Toxocariasis. In: Gillespie, SH, Pearson, RD, editors. Princ. Pract. Clin. Parasitol. London: John- Wiley.
- Tedford, E, Mc Conkey, G, 2017:** Neurophysiological changes induced by chronic *Toxoplasma gondii* infection. Pathogens 6:19.
- Telgt, DS, van der Ven, AJ, Schimmer, B, 2005:** Serious psychiatric symptoms after chloroquine treatment following experimental malaria infection. Ann. Pharmacother. 39:551.
- Tran, TM, Browning, J, Dell, M, 2006:** Psychosis with paranoid delusions after a therapeutic dose of mefloquine: A case report. Malar. J. 5:74.
- Tyebji, S, Seizova, S, Hannan, AJ, Tonkin, C J, 2019:** Neuroscience and biobehavioral reviews toxoplasmosis: A pathway to neuropsychiatric disorders. Neurosci. Biobehav. Rev. 96:72.
- Verma, R, Anand, KS, Chandra, M, 2011:** Neurocysticercosis association with cognitive and aberrant behavioural symptoms: A case report and review. J. Behav. Brain Sci. 1: 229.
- Vigo, D, Thornicroft, G, Atun, R, 2016:** Estimating the true global burden of mental illness. Lancet Psychiat. 3:171.
- Vilar-Pereira, G, De Souza Ruivo, LA, Lannes-Vieira, J, 2015:** Behavioral alterations are independent of sickness behavior in chronic experimental Chagas disease. Mem. Inst. Oswaldo Cruz. 110:1042.
- Vincent, IM, Daly, R, Courtioux, B, Cattanaach, AM, Biéler, S, 2016:** Metabolomics identifies multiple candidate biomarkers to diagnose and stage human African Trypanosomiasis. PloS Neg. Trop. Dis. 10, 12:e0005140
- Webster, JP, Mconkey, GA, 2010:** *Toxoplasma gondii*-altered host behavior: Clues as to. Folia Parasitol. 56:95.
- Wichers, MC, Koek, GH, Robaey, G, Verkerk, R, Scharpé S, et al, 2005:** IDO and interferon- α -induced depressive symptoms: A shift in hypothesis from tryptophan depletion to neurotoxicity. Mol. Psychiat. 10, 6:538.
- Wiwanitkit V, 2014:** Dementia and neurocysticercosis. Acta Neurol. Taiwanica 23:1.
- WHO 2018:** World Chagas disease (American Trypanosomiasis) Report 2018. Chagas disease is available at: https://www.who.int/health-topics/chagas-disease#tab=tab_1.
- WHO 2022a:** World Malaria Report 2022. Malaria: <https://www.who.int/news-room/fact-sheets/detail/malaria>.
- WHO, 2022b:** Report 2022. Trypanosomiasis, human African sleeping sickness available at: [https://www.who.int/newsroom/fact-sheets/detail/trypanosomiasis-human-african-\(sleeping-sickness\)](https://www.who.int/newsroom/fact-sheets/detail/trypanosomiasis-human-african-(sleeping-sickness)).
- Xiao, J, Prandovszky, E, Kannan, G, Pletnikov, MV, Dickerson, F, Severance, EG, Yolken, RH 2018:** *Toxoplasma gondii*: Biological parameters of the connection to Schizophrenia. Schizophr. Bull. 44, 5:983
- Ynceboz, M, Inceboz, T, 2021:** Toxoplasmosis and neuropsychological effects. Turk. Parazit. Derg. 45:49.
- Yüksel, P, Kocazeybek, B, 2013:** Do microorganisms have a role in neuropsychiatric diseases? Flora 18:59.
- Zádor, F, Nagy-Grócz, G, Kekesi, G, Dvórácskó, S, Szűcs, E, et al, 2019:** Kynurenines and the endocannabinoid system in schizophrenia: Common points and potential interactions. Molecules 24:3709.
- Zhang, Y, Träskman-Bendz, L, Janelidze, S, Langenberg, P, Saleh, A, et al, 2012:** *Toxoplasma gondii* immunoglobulin G antibodies and nonfatal suicidal self-directed violence. J. Clin. Psychiat. 73:1069.