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Review article

Toxoplasma gondii: A possible etiologic agent for Alzheimer's disease

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ABSTRACT

Toxoplasma gondii (*T. gondii*) is one of the most pervasive neurotropic pathogens causing different lesions in a wide variety of mammals as intermediate hosts, including humans. It is estimated that one-third of the world population is infected with *T. gondii*; however, for a long time, there has been much interest in the examination of the possible role of this parasite in the development of mental disorders, such as Alzheimer's disease (AD). *T. gondii* may play a role in the progression of AD using mechanisms, such as the induction of the host's immune responses, inflammation of the central nervous system (CNS), alteration in the levels of neurotransmitters, and activation of indoleamine-2,3-dyoxigenase. This paper presents an appraisal of the literature, reports, and studies that seek to the possible role of *T. gondii* in the development of AD. For achieving the purpose of the current study, a search of six English databases (PubMed, ScienceDirect, Web of Science, Scopus, ProQuest, and Google Scholar) was performed. The results support the involvement of *T. gondii* in the induction and development of AD. Indeed, *T. gondii* can be considered a risk factor for the development of AD and requires the special attention of specialists and patients. Furthermore, the results of this study may contribute to prevent or delay the progress of AD worldwide. Therefore, it is required to carry out further studies in order to better perceive the parasitic mechanisms in the progression of AD.

1. Introduction

Dementia is a neurodegenerative disease characterized by progressive impairment in cognitive and functional abilities and behavioral and psychological symptoms [1]. Alzheimer's disease (AD) is the most common type of dementia, including about two-thirds of all cases of dementia [2]. Firstly, AD was described a century ago, and its etiology and pathogenesis have not yet been properly understood [3]. There are two types of AD, namely one early-onset familial type associated with genetic mutations and the other very common late-onset form, which is a multifactorial process that may involve infectious co-factors [4]. The AD is characterized by dystrophic neuritis [5], irreversible loss of neurons in the cortex and hippocampus [6], granulovacuolar degeneration [7], amyloid-beta (Aβ) plaques caused by the aggregation of Aβ1-42 peptide, neurofibrillary tangles (NFTs) formed by a microtubule-associated protein [8, 9], synaptic dysfunction, microgliosis [10], reactive astrocytosis Hirano bodies [10], neuropil threads (i.e., curly fibers) [11], and cerebral atrophy [5]. In addition, the transport of oxygen to the brain and its reduction in the bloodstream may act as a mechanism in the etiology of AD [12]. However, NFT and Aβ are not specific to AD and are produced in other conditions of the central nervous system (CNS) [13]. Patients suffer from short-term memory loss, verbal memory decline, mood swings, loss of motivation, the disorder in the ability to perform daily activities, problems of judgment, decision-making, and plan-making, the general decline in performance, and reduction of cognitive abilities and acquired skills [6, 9, 14, 15, 16]. Furthermore, these patients often show behavioral and psychological symptoms of dementia (BPSD), including depression, anxiety, and psychosis [17, 18]. The BPSD is related to the degree of functional and cognitive impairment and worsens the disability and care burden [17, 19]. There are no definitive treatments to stop or reverse the effects of AD; most patients die within 2–3 years after diagnosis [20], and pneumonia is the most common cause of mortality in people with AD [21]. Risk factors associated with the development of AD include age, the accumulation of Aβ and tau proteins, genetic diversity, such as the *presenilin-1* and *Apolipoprotein E* (ApoE) genes, family history, cardiovascular risk factors, and infectious diseases (i.e., viral, fungal, bacterial, and parasitic) [22, 23, 24, 25].

Toxoplasma gondii (*T. gondii*) belonging to the phylum Apicomplexa is a neurotropic protozoan parasite with worldwide distribution infecting various warm-blooded mammals as intermediate hosts (e.g., one-third of

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the human population), and cats are the final hosts of this parasite [26]. Intermediate hosts acquire *T. gondii* infection in various ways, including the ingestion of vegetables or water contaminated with oocysts shed in the feces of infected felids, ingestion of tissue cysts of insufficiently heated meat, solid organ transplantation, blood transfusion, and vertical transmission from mother to the fetus [27]. The clinical signs (e.g., encephalitis, chorioretinitis, and pneumonitis) of *T. gondii* infection appear in immunocompromised hosts. Most of the primary infections are usually benign in the immunocompetent hosts. Although different systematic review and meta-analysis studies suggested that *T. gondii* infection could be associated with psychiatric and neurological disorders [28, 29], the results revealed that the seroprevalence rates of toxoplasmosis were higher in various mental disorders, including schizophrenia [30], obsessive-compulsive disorder [31], bipolar disorder [32], addiction [30], epilepsy [33, 34], suicide attempts [35, 36], traffic accidents [35, 37], and headache [38]. Neurological disorders caused by *T. gondii* may be the result of the persistence of parasitic cysts in the CNS, host immune response to the parasite, and damage caused by the primary infection [39]. *T. gondii* has a special tendency to the CNS and can infect a variety of brain cells, including neurons, Purkinje cells, and microglial cells [40]. As the cysts grow, the host cells degenerate. Furthermore, these cysts may rupture and release bradyzoites, which can differentiate into tachyzoites. In the absence of the immune system, the surrounding cells are invaded and killed by these tachyzoites [41]. Since bradyzoites can inhibit cell apoptosis, the formation of tissue cysts permits *T. gondii* to induce long-term infection [39]. A chronic infection, along with an increase in interferon-gamma (IFN-γ) production, as the main cytokine for immunological defense against *T. gondii*, decreases the tryptophan and serotonin levels. Moreover, decreased serotonin levels are associated with many cognitive impairments in rodents and humans [1]. The IFN-γ is produced following *T. gondii* infection and leads to the degeneration of dopamine-producing neurons [42]. In addition, *T. gondii* infection increases the activity of the enzyme tyrosine hydrolase (encoded by parasite genes), which releases dopamine [1]. Dopamine is an important neurotransmitter in the brain playing a significant role in the etiology of AD the levels of which reduce in this disease [43]. Given the relatively high prevalence of *T. gondii* and the importance of the role of *T. gondii* infection in the development of mental disorders, the present study was conducted to investigate the current state of knowledge about the role of *T. gondii* infection as an etiologic agent in the progression of AD. In addition, the results of this study may contribute to the prevention, diagnosis, and treatment of AD worldwide.

2. Design

A narrative review was undertaken to allow a comprehensive analysis of the literature published in electronic-based journal articles. This type of review is effective in cases where there is a large amount of data and it is difficult to summarize these data because different studies are being analyzed.

2.1. Literature search strategy

For this review, we searched published studies using six English databases, including PubMed, ScienceDirect, Web of Science, Scopus, ProQuest, and Google Scholar, from their inception until April 2020. The search terms used were: ''*Toxoplasma gondii*'', ''Alzheimer's disease'', ''dementia'', and ''risk factor''. Finally, 68 studies (26 articles evaluating the risk factors involved in AD and toxoplasmosis, 21 review articles, 14 articles evaluating the association between AD and *T. gondii* in humans, and 7 animal models) were selected for evaluation using their full texts.

2.2. Infectious agents and co-infection in AD

Infectious agents that may be involved in AD include viral (e.g., Herpes simplex virus-1 (HSV-1) [44,45], *cytomegalovirus* (CMV) [46], *Varicella zoster virus* [47], *Epstein-Barr virus* [48], human herpesvirus (HHV)-6 [48], hepatitis C virus (HCV) [49], and HHV-2 [50]), fungal (e.g., *Candida famata*, *Candida albicans*, *Candida glabrata*, and *Syncephalastrum racemosum* [51, 52, 53], bacterial (e.g., spirochetes [54, 55], *Borrelia burgdorferi* [56, 57], *Chlamydia pneumonia* [4, 58, 59], *Treponema pallidum* [60], *Helicobacter pylori* [61, 62], actinomycetes [48], and *Propionibacterium acnes* [63], and parasitic (e.g., *T. gondii* [64, 65, 66, 67], *Toxocara* spp. [68], and *Taenia solium* [69]).

Co-infection of two or more infectious agents may also occur and affect the initiation or exacerbation of AD, such as viruses and parasites [70, 71], bacteria and parasites [72], and bacteria, viruses, fungi, and parasites [73]. Gale *et al.* suggested the relationship between viruses [HSV-1, HSV-2, CMV, HAV, hepatitis B virus (HBV), and HCV], parasites (*Toxocara* and *Toxoplasma*), and cognitive function in 5662 young to middle-aged subjects. Of the eight pathogens, HSV-1, CMV, and hepatitis A virus (HAV) had a strong association with decreased cognitive outcomes. In addition, HSV-2, HBV, toxoplasmosis, and toxocariasis decreased cognitive function, but less severe than the first group. HCV showed the weakest association [70]. Another study showed that individuals with higher levels of IgG antibodies against HSV-2, CMV, and *T. gondii* were associated with cognitive decline over a 5-year follow-up period, but HSV-1 was not [71].

In another study, Gale *et al.* showed that joint infection by bacteria (*Helicobacter pylori*) and parasites (*T. gondii*) increased susceptibility to cognitive deficits compared to either *Helicobacter pylori* or latent toxoplasmosis alone [72]. In addition, the results of a study for the presence of early and latent forms of HSV-1, *Borrelia burgdorferi*, *Chlamydia pneumoniae*, *Candida* species, and *T. gondii* among 10 brain samples from AD patients displayed the presence of several fungal structures using immunohistochemistry and the presence of several bacterial species using nested PCR. Nonetheless, co-infection of bacteria, viruses, fungi, and parasites was not confirmed [73].

2.3. Possible association between T. gondii infection and AD

A recent meta-analysis study showed that the risk of AD increased 1.53 times among individuals with *T. gondii* infection compared with the control group (OR = 1.53; 95% CI: 1.07–2.18) [74]. In this meta-analysis, eight studies and nine datasets were studied (Table 1). A total of 3,239 subjects containing 360 cases (48.61% positive for toxoplasmosis) and 2879 controls (22.85% positive for toxoplasmosis) were analyzed. It is worth noting that four articles focused on the prevalence of *T. gondii* infection in any psychiatric disorder, including AD, compared with healthy individuals [75, 76, 77, 78], while the other four articles focused only on AD [64, 65, 66, 67]. A study in 2018 demonstrated that seroprevalence of *T. gondii* infection in participants with dementia and those without dementia were 64.0% and 63.4%, respectively. Therefore, no significant association was found between *T. gondii* seroprevalence and dementia (OR = 1.0) [1]. Also, in a case-control survey in 2019, IgG antibodies were measured against *T. gondii* infection in psychiatric patients in China. In this study, four out of 44 (9.1%) individuals with dementia were positive for IgG antibodies [79].

2.4. Role of age in AD

Aging is the most important risk factor for AD [25]. For example, the frequency rates of AD are reported as approximately 15% and 44% in people within the age range of 65–74 and over the age of 80 years in industrialized countries, respectively [80]. The disease is expected to quadruple by 2050 due to an increase in the number of people over the age of 85, and by then 1 in 85 individuals worldwide will be living with the disabling disease [81, 82]. Most cases of *T. gondii* infection in humans are acquired after birth. Interestingly, the prevalence of *Toxoplasma* increases with age [83], such as in Panama, the seroprevalence of *T. gondii* has been reported to be 13% at age 6 years and 90% at age 60 years [84, 85]. The reason is that aging increases the possibility of exposure to the

parasite. Therefore, the risk of developing AD and *Toxoplasma* increases with age.

2.5. Role of sex in AD

The specific parasite-driven behavioral changes appear to vary depending on the sex of the intermediate host [86, 87]. One study reported sex differences in clinical phenotype and AD progression, indicating that women are more protected than men in the prodromal phases but later show cognitively faster and higher rates of brain atrophy [88]. The results of an experimental study showed that the host sex plays an important role in determining variable brain and behavioral changes after *T. gondii* infection. In female mice, *T. gondii* infection alters the expression of genes involved in the development of the forebrain, neurogenesis, and sensory-motor coordination, but in male mice, the infection modulates genes associated with olfactory function [87]. The manipulation of host behavior by parasite causes infected male rats become more attractive to females. Also, uninfected females spend more time near infected males and give them more access to fertility and thus created more ways for sexual transmission by the parasite itself [89]. *T. gondii*-stimulated IFN-γ can potentially affect the attraction and loss of fear for predator odor in rodents [90].

2.6. Impact of genetic on AD

One of the factors associated with the development of AD is genetic variants such as *presenilin* and ApoE genes [91]. Out of 26,846 genes in the human genome, 10.4% of them are involved in *T. gondii* the host/-pathogen interactome. Results of the Kyoto Encyclopedia of Genes and Genomes pathway analysis revealed that the number of genes in each pathway in AD is 52 [92]. Ngô *et al.* indicated the overlap between the number of susceptibility genes in various diseases and the *T. gondii* interactome. For instance, the number of susceptibility genes in AD is 432, 118 (27.3%) of which are involved in *T. gondii* interactome [93].

T. gondii is unable to produce cholesterol de novo, the cholesterol of host neuron cells consumes. The nerve cells are deprived of cholesterol leading to the ability of the parasite to increase dementia [94]. The ApoE, a polymorphic protein, has three main isoforms (i.e., ApoE2, ApoE3, and ApoE4) and plays a role in the neuronal transport of cholesterol. Cholesterol is an essential substance for axon growth and synaptic arrangement. Cholesterol is also involved in rebuilding occasions that are important for memory, learning, development, and nerve repair [95].

The ApoE is 34 kDa in size and composed of 299 amino acids [96]. The host mitochondria, endoplasmic reticulum, and cell lipid biosynthetic apparatus surround the parasitophorous vacuole membrane of *T. gondii* [97]. Other functions of ApoE include the absorption of lipids produced after the degeneration of neurons and their redistribution in cells requiring lipids to repair membranes, proliferate, or regenerate new axons [98].

Yahya *et al.* investigated the effect of ApoE genotypes on dementia in relation to neurodegeneration in latent toxoplasmosis in elderly peoples. The results indicated that *Toxoplasma* positive patients are reported with a higher risk of developing dementia regardless of ApoE4 carriage [99]. The ApoE4 is strongly associated with AD [100] the frequency rates of which are 15% and 40% in healthy subjects and individuals with AD, respectively [101]. Most of the plasma ApoE is formed in the liver and macrophages, and the ApoE in the CNS is locally produced [102]. The presence of the ApoE4 allele increases the prevalence of AD and reduces the age of AD onset [101]. Based on the evidence, it was observed that memory and learning deficits from mild to severe were present in ApoE-null mice [103, 104]. Memory impairment is associated with cholinergic defects, indicating the importance of the role of ApoE in cognition and memory [105, 106]. In addition, Aβ deposition as senile plaques is more common in individuals with the ApoE4 allele, compared to those without this allele [107].

2.7. Role of inflammatory responses produced by T. gondii in AD

Inflammatory responses are the innate defense against *T. gondii* infection [108]. Infection with *T. gondii* initiates the T helper type 1 (Th1) cell-mediated immune response releasing several cytokines, such as IFN-γ, interleukin-12 (IL-12), interleukin-1, interleukin-6 (IL-6), and tumor necrosis factor (TNF) [109]. Inflammatory cytokines and mediators have both protective and pathological effects [110, 111]. In addition to inhibiting the proliferation and spread of *T. gondii*, these factors can cause significant damage to non-infected neurons. These factors also affect the function of neurotransmitters and synaptic transmission [112, 113]. Neuroinflammatory processes, oxidative stress, and vascular factors are effective agents in the pathogenesis of AD [114, 115, 116]. Almost 20 years ago, the innate inflammatory responses in AD have been described [66]. It has been shown that taking nonsteroidal anti-inflammatory drugs by patients significantly reduces the risk of developing AD [117]. Many genetic risk factors have been identified for AD which have a role in the immune system, such as the triggering

Table 1. Description of the studies included looking for an association between toxoplasmosis and AD.

No	First author	N	Alzheimer$^+$ (n)	Alzheimer$^-$ (n)	Alzheimer$^+$ & T$^+$ (n, %)	Alzheimer$^-$ & T$^+$ (n, %)	Age (years ± SD)	Sex
1	Alvarado-Esquivel *et al.*	182	2	180	2 (100%)	16 (8.9%)	P: ≥16 C: 16–54	P: (F:–, M:–) C: (F:55, M:125)
2	Kusbeci *et al.*	71	34	37	15 (44.1%)	9 (24.3%)	P: 68.05 ± 15.98 C: 62.91 ± 5.89	P: (F:15, M:19) C: (F:16, M:21)
3	Cong et *al.*	478	33	445	5 (15.15%)	55 (12.36%)	P: 16–91 C: 16–91	P: (F:–, M:–) C: (F:238, M:207)
4	Cong et *al.*	463	18	445	3 (16.66)	55 (12.36%)	P: 16–91 C: 16–91	P: (F:–, M:–) C: (F:238, M:207)
5	Menati Rashno *et al.*	174	87	87	58 (66.6%)	49 (56.32%)	P: 78.17 ± 10.38 C: 45.63 ± 17.45	P: (F:40, M:47) C: (F:26, M:61)
6	Mahami-Oskouei *et al.*	150	75	75	46 (61.3%)	47 (62.6%)	P: 56-93 C: 56–90	P: (F:41, M:34) C: (F:–, M:–)
7	Zaki *et al.*	166	4	162	2 (50%)	24 (14.8%)	P: 19-67 C: 17-64	P: (F:–, M:–) C: (F:68, M:94)
8	Perry *et al.*	219	105	114	43 (40.95%)	38 (33.33)	P: 80.4 ± 7.2 C: 79.7 ± 7.3	P: (F:57, M:48) C: (F:56, M:58)
9	Flegr and Horáček	1336	2	1334	1 (50%)	365 (27.36%)	M: 35.6 ± 12.4 F: 32.9 ± 12.3	P: (F:2, M:0) C: (F:729, M:240)

AD$^+$: individuals with Alzheimer's disease, AD$^-$: individuals without Alzheimer's disease, AD$^+$ & T$^+$: individuals with Alzheimer's disease and *Toxoplasma* positive, AD$^-$ & T$^+$: individuals without Alzheimer's disease and *Toxoplasma* positive, P: patient, C: control, F: female, M: male, N: number.

receptor expressed on myeloid cells 2. Furthermore, genome-wide association studies showed that there is an immune system dysfunction in AD [118, 119]. Although inflammation is not usually the cause of neurodegenerative diseases, animal models have demonstrated that sustained inflammatory responses in microglia and astrocytes contribute to disease progression. These inflammatory responses may play a role in the development of neuronal degeneration by the production of inflammatory molecules, such as IFN-γ, tumor necrosis factor-alpha (TNF-α), and interleukin-1 beta (IL-1**β)** [66, 120].

In patients with AD, a cognitive decline following systemic inflammation occurs at least 6 months after the onset of the disease and an increase in serum levels of TNF [121]. In addition, a systematic review and meta-analysis study reported that the common odds ratio of anti-*T. gondii* immunoglobulin G [122] antibody in patients with AD are 1.53 times greater, compared to those reported for controls, indicating that *T. gondii* infection may play a role in the pathogenetic mechanisms of AD [74]. The deposition of Aβ peptides triggers the activation of macrophages, microglia, lymphocytes, and astrocytes, which in turn release different inflammatory mediators [123]. In a study carried out by Jung *et al.*, it was shown that the levels of anti-inflammatory cytokines, interleukin-10 (IL-10), and transforming growth factor-beta (TGF-β) in brain tissues were significantly higher in *T. gondii*-infected Tg2576 mice than uninfected mice [124]. Transforming growth factor-beta1 (TGF-β1) is a major regulator of the brain's response to damage and inflammation involved in *in vivo* Aβ deposition and AD pathogenesis [125]. The accumulation of Aβ in the cerebral blood vessels of mice expressing human amyloid precursor protein (hAPP) and TGF-β1 is significant, but not in parenchymal plaques. This decrease is associated with strong activation of microglia and an increase in inflammatory mediators. The TGF-β1 strongly decreases the overall cerebral amyloid plaque burden by preventing the formation of neuritic plaques in the brain parenchyma [125]. Moreover, the activation of cell-surface receptors expressed on neurons accompanied by a proapoptotic cell death pathway and neurotoxicity through regulatory activity on glial cells are performed by pro-inflammatory cytokines [126]. The activation of glial cells surrounding senile plaques in the brain impairs synaptic function and neurological death leading to cognitive impairments [25]. The inhibition of the inflammatory response may result in slowing and reversing the progression of AD [127]. The well-being of the blood-brain barrier leads to the recruitment of peripheral blood leukocytes and their active participation in local brain tissue inflammation. Leukocytes are also involved in the release of inflammatory agents and exacerbation of the inflammatory state and AD-related pathologies [116, 128, 129].

Experiments have shown that inflammatory mediators (e.g., cytokines, complement components, various free radicals, and nitric oxide [NO]) by different means may stimulate amyloid precursor protein processing leading to the pathological progression of AD [130, 131]. The activation of indoleamine-2,3-dioxygenase enzyme (IDO), activation of mitogen-activated protein kinase pathways, alteration in the activity of the tetrahydrobiopterin (BH4) enzyme, excitotoxicity, and oxidative stress are mechanisms used by these cytokines and inflammatory mediators during toxoplasmic encephalitis to affect neurotransmitters [132].

2.8. Effect of nuclear factor-kappa B activation modulated by T. gondii on AD

High levels of nuclear factor-kappa B (NF-κB) mediated by IL-1β, IL-6, and TNF-α cytokines were reported in the damaged tissue, serum, and cerebrospinal fluid of patients with AD [133, 134, 135]. The NF-κB, a critical regulator of immune and inflammatory responses, is a transcription factor whose activity is modulated during *T. gondii* infection [136, 137]. The NF-κB signaling by various mechanisms in neurons, microglia, and astrocytes accelerates the progression of neuroinflammation to neurodegeneration in AD [138]. The activation of NF-κB and upregulation of target genes with pro-survival functions occur following *T. gondii* infection [139]. The inhibition of NF-κB target genes involved in inflammation allows the pathogen to escape from the immune system and create a safe environment for the replication of the parasite. In fact, the activation of NF-κB prevents the death of infected cells resulting from apoptosis [140].

2.9. Role of neurotransmitters released by T. gondii in AD

Neurotransmitters are defined as a diverse group of chemical messengers in the brain transmitting signals from one neuron to the next [141]. Impairment in the metabolism of neurotransmitters, transporters, and their receptors is accompanied by a wide range of pathological manifestations [142]. Some neurotransmitters play an important role in the etiology of AD, including dopamine, acetylcholine, and glutamate. The amounts of these neurotransmitters reduce in AD [43, 142, 143]. The IFN-γ is an inflammatory cytokine released following *T. gondii* infection and destroys dopamine-producing neurons [42]. The internal parts of the brain's dopaminergic cells are mainly involved in movement functions, motivation, and working memory [144]. Moreover, cytokines produced against *T. gondii* are able to decrease the concentration of BH4, involved in the synthesis of dopamine, and consequently reduces access to dopamine in different areas of the brain [145, 146]. In addition, the reduced expression of genes within the dopamine pathway, such as D1-like dopamine receptors (i.e., dopamine receptor D1 and dopamine receptor D5), was observed in rodents infected with *T. gondii* [147]. Moreover, the infection with *T. gondii* leads to aberrant dopamine signaling [148]. *T. gondii* can also disrupt dopamine signaling by altering the expression of micro-ribonucleic acids-132 (miR-132) [141]. Micro-ribonucleic acids (mRNAs) are a class of small non-coding RNAs that can regulate gene expression, stability, and translation of up to 60% of protein-coding mRNAs [149]. Numerous mechanisms of the nervous system, such as the regulation of neuronal migration and differentiation, synaptic flexibility, and adult neurogenesis are regulated by miRNAs [150]. The dysregulation of miR-132 expression can be associated with AD in humans and animals [141]. The expression of miR-132 decreases during chronic *T. gondii* infection and increases during acute infection [147, 151]. Moreover, IFN-γ produced by natural killer (NK) cells during *T. gondii* infection induces tryptophan degradation through IDO activation [152, 153]. This mechanism increases the concentration of quinolinic acid (QA) [55] and kynurenic acid (KA) [154]. KA is an antagonist of N-Methyl-D-aspartic acid (NMDA) for glutamate and α7 nicotinic acetylcholine receptor (α7nAChR) for acetylcholine. These two receptors play an important role in learning, memory, and cognitive processes [155, 156]. On the one hand, QA, an NMDA agonist, produced by microglia, binds to glutamate N-Methyl-D-aspartic acid receptors (NMDARs) [154, 157]. Glutamate mediates the release of NO from its NMDA receptor, and NO is involved in learning and memory processes (Figure 1) [158]. During *T. gondii* infection, NO levels in various organs of infected mice (i.e., liver, brain, spleen, and serum) increased significantly [159]. Increased NO can be toxic and cause cell damage in the brain due to the formation of molecules with toxic effects, such as peroxynitrite [160]. The NO is an important inflammatory mediator directly related to the control of parasitemia and prevents parasite proliferation [161]. NO production due to inflammation and resulting oxidative stress has been implicated in the etiology of AD [162, 163]. The chronic infection of *T. gondii* reduces the expression of glutamate transporters (i.e., glutamate transporter-1) in glial cells and leads to an increase in extracellular glutamate [164]. Alterations in the function or expression of the glutamate transporters are shown in the pathogenesis of AD [165]. Glutamate transporters can play a role in memory and learning [166]. *T. gondii* infection increases the level of acetylcholinesterase in the brain of infected mice [167]. The release of this enzyme is one of the causes of AD inducing impaired spatial memory. The gradual impairment of memory, especially spatial memory, is one of the primary symptoms of AD reducing the amount of acetylcholine as a result of the high release of acetylcholinesterase is an enzyme attached to the membrane hydrolyzing acetylcholine [143, 168]. In addition, the release of acetylcholinesterase

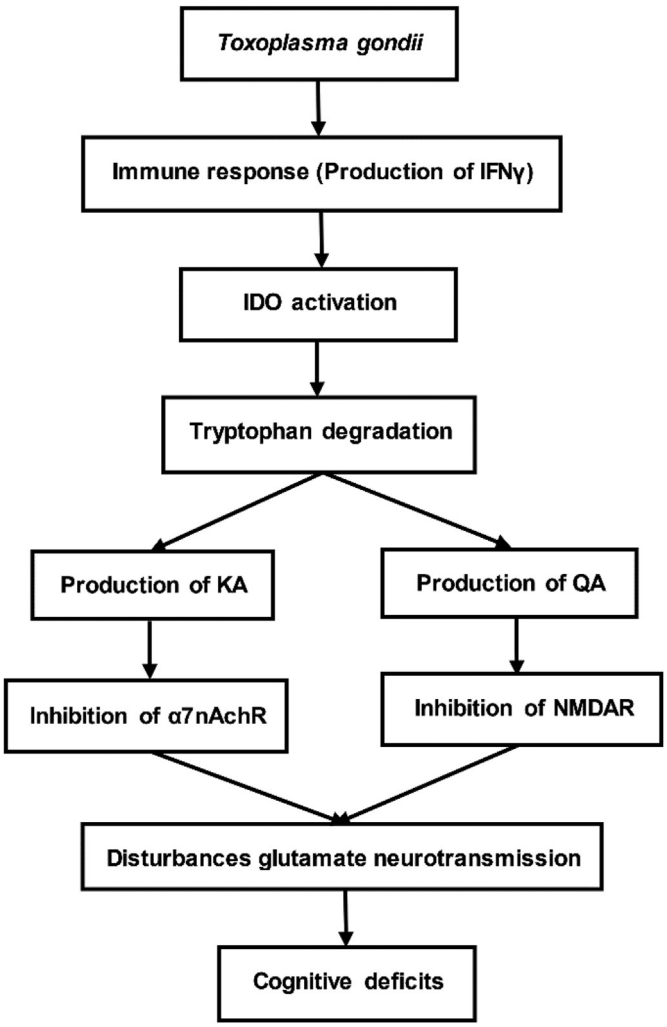

Figure 1. The possible role of IFN-γ in neurogenesis in AD. IFN-γ: interferon-gamma, IDO: indoleamine 2,3-dioxygenase, KA: kynurenic acid, QA: quinolinic acid, NMDAR: N-Methyl-D-aspartic acid receptor, and α7nAChR: α7 nicotinic acetylcholine receptor.

from plaques and toxic effects of Aβ deposits on brain cells lead to the formation of inflammatory tissue in the brain [67]. Gamma-aminobutyric acid (GABA) is another neurotransmitter identified in adult neural tissues and produced from the conversion of glutamate through glutamic acid decarboxylase 67 in the presynaptic area of GABAergic neuron terminals [169]. Defects in GABAergic signaling are associated with AD [82].

2.10. Role of C1q activated by T. gondii in AD

C1q is one of the immune proteins of the classical complement system that is involved in synaptic pruning and elimination during neurodegenerative processes and etiology of some neurological diseases, such as AD. Other roles of C1q include the modulation of cytokine production, induction of transcription factors in myeloid cells, and increased phagocytosis of apoptotic cells [170, 171, 172]. C1q has been reported with Aβ deposits in humans [173, 174] with AD and murine models of AD [170, 175].

Xiao *et al.* showed that the levels of C1q mRNA and proteins in the brain of mice infected with *T. gondii* increased significantly [176]. The loss of synaptic complexity can be a part of the damage caused in neurons due to the activation of the complementary system by the host as a response to parasite invasion [141]. In addition, C1q may accelerate the progression of AD. A murine model of AD showed that a complete genetic deficiency of C1q reduced AD-like gliosis and neural integrity [177].

2.11. Activation of hypothalamic-pituitary-adrenal axis related to T. gondii in AD

An auxiliary factor for the changes caused by infection with *T. gondii* is the activation of the hypothalamic-pituitary-adrenal (HPA) axis. However, there has been no evidence between the change in host behavior and activation of the HPA axis. Chronic immune response leads to host stress responses, which in turn can cause the activation of the HPA, regulating homeostasis in the body [178].

Blood glucocorticoid concentrations increase by HPA activation, which in turn is associated with neurodegeneration and synapse regression [179]. Increased glucocorticoid concentration has been linked to many psychiatric disorders, such as AD [180]. The chronic action of glucocorticoids causes brain aging, especially of the hippocampal neurons [180]. The hippocampal neurons are involved in the negative feedback inhibition of the HPA axis. It is assumed that these neurons lose negative feedback control with aging and lead to increased plasma corticosterone and adrenal activity [181]. High levels of corticosterone have been shown in the AD mouse models to be involved in insulin resistance and memory impairment [182].

2.12. Toxoplasma pathways in AD and multiple sclerosis (MS)

T. gondii has a strong tendency toward the central nervous system, where tachyzoites can invade microglia, astrocytes, and neurons in form of cysts causing chronic infection [183, 184]. Innate immunity-mediated neuroinflammation and cellular immunity are involved in the pathogenesis of neurodegenerative diseases such as MS (one of the most common diseases of CNS), and AD [185, 186]. However, $CD4^+$ T cells have been shown to be a major pathogen of MS and are also involved in the development of AD [187, 188]. On the other hand, the available data suggest that CD8+ T cells are the predominant type of T cells in MS brain lesions and the development of neurocognitive impairments in AD patients and transgenic mouse AD models [189, 190]. Therefore, it may be hypothesized that CD8+ T cells contribute to the development of neurocognitive impairments in MS and AD. *T. gondii* induces a very strong Th1 response by the production of pro-inflammatory mediators such as IFN- γ and NO [111]. The MS is characterized by an inflammatory response associated with the production of Th1-type cytokines, such as IFNγ [191]. IFNγ, the main responsible cytokine for immunological defense against *T. gondii,* is released following *Toxoplasma* infection which leads to tissue injury through the production of NO and degeneration of dopamine-producing neurons [192, 193]. Therefore, this parasite may be one of the important infectious agents involved in neurological diseases, such as AD [192]. The development of typical brain lesions in AD is associated with a variety of neurotoxic Aβ peptides [194]. However, in MS, despite expression of amyloid precursor protein [58], reflecting axonal damage [195], and the increased levels of soluble α-APP and β-APP, intermediate products of APP proteolysis [196], amyloid plaques were not found in brain lesions [122, 197, 198, 199]. NMDAR is very important in both animal AD and MS models [200, 201]. In addition, specific activation of extrasynaptic NMDARs in animal AD models increases amyloidogenesis and Aβ release [202] and tau phosphorylation [203, 204], leading to disease progression [205].

2.13. Role of N-Methyl-D-aspartic acid receptors related to T. gondii in AD

The NMDAR plays a role in synaptic plasticity, cognition, learning, and memory function. The NMDAR dysfunction is involved in the pathophysiology of AD [206]. In fact, this receptor mediates the strength of synaptic transmission in response to neural activity [207]. *T. gondii* leads to the loss of NMDAR through the stimulation of Aβ immunoreactivity. The NMDAR loss results in the disruption of feedback inhibition signals

by NMDA, GABA, and vesicular glutamate transporters, increase of glutamate levels in the synaptic cleft, neurotoxicity, and neurodegeneration. The Aβ reduces the surface expression of NMDARs by increasing their endocytosis [208]. Reactive oxygen species are activated in the brain by *T. gondii* infection, resulting in the release of IFNγ [108]. Reactive oxygen species stimulate the production of Aβ 1–42 [209]. These reactive oxygen species bind to NMDAR and lead to the abnormal activation of NMDAR [210]. This abnormal activation leads to a significant increase in Ca^{2+} entry into postsynaptic neurons. This increases the presynaptic glutamate release, resulting in neuronal damage, decreased vesicular glutamate transporter 2 (VGLUT2), loss of olfactory sensitivity, and memory disorders (i.e., early signs of AD) [82]. Vesicular glutamate transporter 1 (VGLUT1), VGLUT2, and vesicular glutamate transporter 3 mediate the uptake of glutamate through synaptic vesicles. The VGLUT1 plays a role in neurotransmission, and VGLUT2 is involved in synaptic flexibility and protection of nerve damage [211].

2.14. Amyloid-beta and heterogeneous effects of T. gondii on AD

In AD, there is an increase in the amount of soluble and insoluble Aβ, mainly in amyloid plaques in the form of Aβ42 and amyloid angiopathy in the form of Aβ40 [212]. According to the amyloid hypothesis, AD is caused by an imbalance between the production and elimination of Aβ and leads to an increase in the amount of Aβ in the CNS [213]. High levels of Aβ cause neuronal damage and death [212]. In fact, the insufficient function of Aβ transporters at the blood-brain barrier leads to Aβ accumulation in the brain and plaque formation [214]. Moreover, Aβ has potential antimicrobial properties. The production and deposition of Aβ in patients may be due to the stimulation of infectious agents. The Aβ inhibits the proliferation of the influenza virus under *in vitro* conditions [8]. *T. gondii* has heterogeneous effects on AD because the effects of infection depend on the body's immune responses. These responses are due to the interaction between the parasite strain and the genetic mouse model of AD used in studies [141]. In Tg2576 mice (indicating a mutation in the amyloid precursor protein) and 5xFAD mice (indicating a mutation in the amyloid precursor protein and presenilin protein-1), *T. gondii* infection resulted in a decrease in Aß plaque, possibly due to the increased production of anti-inflammatory cytokines (i.e., TGF-β and IL-10). In addition, increased monocytes are able to phagocytose Aß [124, 214]. These neuroprotective effects improved the cognitive capacity of *T. gondii*-infected mice with AD [124]. In a study carried out by Cabral *et al.* using the hAPP AD mouse model, it was reported that only the type II strain of *Toxoplasma* was able to stimulate neurodegenerative changes [215]. In another study, Mahmoudvand *et al.* investigated the effect of *T. gondii* infection on the progression of AD in BALB/c mice. The results of the aforementioned study showed that *T. gondii* infection could exacerbate AD in infected mice receiving a sub-dose of Ab1-42 and cause significant impairment in learning and memory functions [15].

2.15. Effects of sleep disorders produced by T. gondii on AD

Sleep problems increase the risk of dementia [216, 217, 218]; however, AD is usually diagnosed some years after the onset of pathological changes in the brain [219]. Disorders of sleep and circadian rhythm often affect the quality of life and safety of people with AD [219]. It has been suggested that sleep disorders may be the early signs of dementia and Aβ pathology and may occur before the onset of cognitive symptoms in AD. Self-reported sleep disturbances are associated with an increased future risk of dementia over 1–9 years [220].

According to the evidence, the sleep-wake cycle can directly affect the levels of Aβ in the brain, and the accumulation of Aβ in the brain triggers a cascade of important events in the pathogenesis of AD. Experimental models have shown that sleep deprivation increases the concentration of soluble Aβ and leads to chronic accumulation of Aβ [219]. The accumulation of Aβ in the brain is one of the first major pathological symptoms in AD and may be a trigger for sleep disorders; however, other factors, such as irregular physical activities or mealtimes of the elderly, exposure to insufficient daylight for institutional care, antidepressants, and medication for hypertension or heart diseases, may also play a role in the severity of sleep problems in patients with AD [219]. The results of two studies examining the relationship between *T. gondii* immunoglobulin G seropositivity and sleep problems have shown that sleep is unlikely associated with mental disorders [221, 222]. However, *T. gondii* may directly affect sleep through dopamine endogenous production [148, 223, 224]. For example, in patients with Parkinson's disease and low levels of dopamine-producing neurons, excessive sleeping is often observed during the day [225, 226]. In addition, *T. gondii* can promote sleep by the induction of the immune system, and immune pathways helping control *T. gondii* in the host play a role in sleep-wake regulation [221]. The levels of two pro-inflammatory cytokines (i.e., IL-12 and TNF) are associated with the control of acute *T. gondii* infection; accordingly, the aforementioned cytokines peak during sleep [227]. In addition, IL-10 prevents excessively active immune responses during infection and peaks during sleep [228, 229]. The reaction between sleep and the immune system improves the fitness of the host by allocating energy to important physiological functions involved in controlling the infection [229]. Sleep strengthens the immune system and increases resistance to parasites [230]. Furthermore, increasing the amount of melatonin at night plays a role in increasing sleep propensity and synchronization of the circadian clock [231]. In addition, melatonin has cytoprotective, antioxidant, and even anti-amyloid effects [231]. The IFN-γ produced by NK cells during *T. gondii* infection induces tryptophan degradation through the activation of IDO [152, 153]. Tryptophan is a precursor of neurochemical mediators, such as melatonin [232]. Among the pathological features of AD are tau tangles that may have negative effects on sleep or circadian rhythms; however, they have not been studied [219].

2.16. Role of zinc related to T. gondii in AD

Zinc (Zn) is a ubiquitous metal found throughout the body, including the brain [233]. Zn deficiency is one of the major causes of immune deficiency [234]. Immunity is directly related to the amount of Zn in cells and tissues, and if Zn is deficient, infections often occur [235]. Zn deficiency has a greater effect on the immune response than other metal elements [234, 235]. Zn increases and activates the number of lymphocytes and is known as the natural mitogen of T-lymphocytes [236, 237]. The levels of IFN-γ, interleukin-2 (IL-2), and TNF-α depend on Zn and Zn-dependent hormones called thymulin.

Kasim Baltaci *et al.* investigated the effects of Zn supplementation on cellular immunity in rats infected with *T. gondii*. In rats infected with *T. gondii* receiving intraperitoneal injections of Zn sulfate at a dose of 3 mg/kg/day for 3 weeks, the total lymphocyte ratios were higher than those of the infected and healthy controls [238]. Dietary Zn deficiency has a direct effect on the Th1 function and consequently increases the production of IFN-γ and IL-2 [239]. About 3,000 human genes are known as encoding for zinc-binding proteins. Due to the different functions of Zn in nerve cells, intracellular Zn concentration is highly regulated because the proper homeostasis of this metal is important in maintaining normal cell processing [240]. Zn is involved in many cellular processes, including neurotransmission, regulation of enzyme activity, regulation of gene expression, and maintenance of protein structure and stability [233]. The intracellular diffusion of Zn is a common toxic event in oxidant-induced neuronal apoptosis. Oxidative stress is an important cause of brain aging and age-related pathology. In addition, oxidative stress-induced cell death is common in many neurological disorders, such as AD. The lack of Zn regulation may play a role in disorders associated with the aging of neurons [233].

3. Conclusion and future perspectives

The aging of the world's population increases the economic and social burden associated with AD and dramatically grows the number of people

with the disease. Multiple studies have shown that *T. gondii* can be a major contributor to AD etiology. Revealing numerous mechanisms involved in host-parasite interaction is essential to a more detailed perception of the possible association between toxoplasmosis and AD. In addition, monitoring anti-*T. gondii* antibodies could help with the assessment of the infection and initiation of appropriate and timely treatment. *T. gondii* ability to enter and stay in the CNS and enhance the chronic inflammatory response plays an important role in initiating and maintaining neuropathogenesis. Systemic and localized inflammation caused by *T. gondii* infection increases neuroinflammation in AD. This outstanding finding may provide new perspectives into explaining the pathophysiological mechanisms of *T. gondii* infection and AD. Although many potential cellular and molecular mechanisms have been identified for the modification of host behavior, the anatomical analysis of the specific cell types and pathways affected by latent cyst formation can provide a better understanding of the way infection affects the behavior of the host. Certainly, valuable advances in further and better analyses of the possible mechanisms of *T. gondii* in the development of AD and the discovery of prophylactic approaches to reduce neuroinflammation associated with aging will be helpful in the prevention and improvement of disease treatment. Moreover, it is required to carry out large-scale studies to elucidate the potential factors affecting parasitic changes in learning and memory functions among rodents and humans.

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