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Parasitic Encephalitis Caused by *Plasmodium Falciparum*, *Trypanosoma Brucei* and *Toxoplasma Gondii*

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Abstract

Various pathogens such as bacteria, virus, and parasites can cause encephalitis. Three human neuropathogenic parasitic protozoa namely *Plasmodium falciparum, Trypanosoma brucei*, and *Toxoplasma gondii*, which have been found to have different complex and yet intriguing mechanisms of infection. *P. falciparum* has been found to invade red blood cells by interaction between parasitized red blood cells and the vascular endothelium through cytoadherence; similarly, parasitic *T. brucei* can infiltrate the brain by penetration through the blood-brain barrier by secreting enzymes cysteine proteases. *T. gondii* parasite's survival is dependent on a balance between host survival and parasite proliferation when it attacks immunocompromised individuals. The clinical manifestations exhibited in each of these parasitic infections remain diverse and so do the treatment prospects. Therefore, in this article, we present an overview of the current understanding of the clinical symptoms, pathogenesis, and immune-mechanism of encephalitis caused by the above causative agents.

Keywords: Encephalitis; *Plasmodium falciparum; Trypanosoma brucei; Toxoplasma gondii*

Introduction

Encephalitis is a kind of severe neurologic syndrome, often associated with chronic illness and death, can occur when an infectious organism or agent invades and multiplies in a person's brain. Infectious agents that can cause encephalitis include bacteria, viruses, fungi, as well as protozoan and metazoan parasites [1]. Cerebral involvement in parasites is an important clinical manifestation for most of the human parasitoses [2], and parasites that have been described to affect the central nervous system (CNS) including cestodes, nematodes, trematodes, and protozoa. Protozoa remain the most widely distributed eukaryotic cells in nature and are receiving increasing attention as human and animal pathogens [3]. Protozoan diseases range from very mild to serious life-threatening. Five species of malarial parasites are infectious to humans, in which *Plasmodium falciparum* is responsible for nearly all of the severe morbidity and mortality in malaria-endemic areas [4]. *P. falciparum* causes cerebral malaria (CM) that can lead to obstruction of microvasculature in the brain via sequestration [5]. African trypanosomiasis, caused by human infective *Trypanosoma brucei gambiense* and *T. b. rhodesiense*, can lead to irreversible neurological system impairment in African regions. *Toxoplasma gondii*, a very common protozoan parasite, causes a mild illness initially followed by a long-lasting latent infection in immunocompetent persons. However, it can develop into fatal toxoplasmic encephalitis (TE) in acquired immune deficiency syndrome (AIDS) patients [6]. The main factor that leads to the high mortality of encephalitis is the incomplete understanding of the pathogenesis and pathophysiology of such parasites. In this article, we focus on *P. falciparum*, *T. gondii*, *T. b. gambiense*, and *T. b. rhodiense*, which can all cross the blood brain barrier (BBB) and lead to consequences of the CNS invasion, and high light the current understanding of their clinical symptoms associated pathogenesis and immunologic mechanism.

Cerebral Malaria (CM)

P. falciparum is one of the most common causes of the CNS infection, which lead to nearly all the neurological complications and deaths. CM forms part of the range of severe malaria, mostly

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infected by children under the age of 5 as well as pregnant women. Case fatality rates range from 15% in adults in Southeast Asia to 8.5% in children in Africa [5]. CM causes neurological disorders such as nystagmus, conjugate gaze palsy, opisthotonus, seizures, and coma [7].

Clinical Symptoms of CM

The clinical hallmark of CM is impaired consciousness with coma, the most severe manifestation [8]. In African children, coma usually develops suddenly with seizure onset, followed by fever. A few children develop coma following progressive weakness and prostration. Systemic complications such as brain swelling, intracranial hypertension, retinal changes, brainstem signs, anemia, metabolic acidosis, electrolyte imbalance, hyperpyrexia or hypoglycemia, and shock are commonly present. The prognosis is grave in deeply comatose patients with shock, severe metabolic acidosis, hypoglycemia, and repeated seizures [9]. In adult patients, the alteration in mental status, icterus, hypoglycemia, disseminated intravascular coagulation, and malarial hepatitis are highly related to the development of severe malaria and mortality [10].

Pathogenic Mechanism of CM

Sequestration of *P. falciparum* in the cerebral microvasculature is the hallmark of CM [11]. Erythrocytic stage is responsible for its occurrence. When *P. falciparum* merozoites invade the red blood cells (RBCs), it exposes to the adhesive proteins on the surface of the infected red blood cells (iRBC), causing iRBCs to stick to the walls of microvasculature via a process called cytoadherence, a special interaction between iRBCs and the vascular endothelium. *P. falciparum* parasite derived proteins presented on the surface of RBCs causing sequestration results from adherence of iRBCs to the endothelial lining of blood vessels [12]. The parasitic sequestered mass increases in size when more iRBCs clump together, which impair perfusion of blood and aggravate coma through hypoxia caused by disability of iRBCs to deform and pass through the brain microvasculature [5]. Study proving that local perfusion is decreased in the eye of children with paediatric cerebral malaria [13]. In those who develop severe brain injury or death, sequestration of iRBCs is more serious; the blood flow obstruction cannot be reversed, thus giving rise to widespread of hypoxia and ischemic injury [14]. As a result of cytoadherence, a few processes such as endothelial activation, release of endothelial micro-particles and apoptosis of host cells occur in the brain. Endothelial activation in blood vessels plays a major role for pathogenesis of CM [15]. Two endothelial regulators have been found, in which angiopoietein-1 (Ang-1) levels were significantly decreased and Ang-2 levels were significantly increased in serum samples of CM patients infected with *P. falciparum*. Severity of disease can be estimated from the ratio between decreased level of Ang-1 or increased Ang-2 in the serum, the promising clinical informative biomarkers for CM [16]. It has been demonstrated that nitric oxide (NO) released in endothelium can regulate Ang-1 and Ang-2, causing vasorelaxation and down-regulation of endothelial adhesion molecules, and reduce thrombosis in the brain [17]. Activated endothelium also over-expresses some of its adhesion receptors such as intercellular adhesion molecule 1 (ICAM-1) and E-selectin on vascular endothelium, which then shed into the blood. ICAM-1 is considered to be the most important cell adhesive molecules upregulated by *P. falciparum* infection and co-localized with iRBCs equestration [18]. Adhesion of iRBCs to endothelial lining reduces the cerebral blood blow, causing obstruction that leads to organ and tissue dysfunction. Coma can occurs as a result of under perfusion in different parts of the brain. *P. falciparum* malaria parasites remodel the host cell by changing its cytoskeleton and insertion of parasite-derived proteins to the membrane of RBCs [19]. Parasitic surface antigens such as *P. falciparum* erythrocyte membrane protein 1 (*PfEMP1*) is thought to be the major virulence factor of CM, which undergoes antigenic variation by mediating its expression on the surface of iRBCs to escape from host defense mechanisms [20]. Presence of variant *PfEMP1* proteins to the host receptors such as ICAM-1 results in different host immune responses [21]. Because histidine-rich protein II (HRPII) binding to brain endothelial cells can result in rearrangement of tight junction proteins and a compromised BBB, suggesting that HRPII contributes to the pathogenesis of CM [22].

It has been reported that increased blood concentrations of pro-inflammatory cytokines are closely associated with CM. Tumor necrosis factor-alpha (TNF-α) secreted by macrophages can upregulate the cytoadherence receptors of vascular endothelium. Synthesis of TNF is a vital sign, which can be either protective by killing the parasites at low concentration or prolonged the parasites to higher level causing hypoglycemia, anemia, and even death [23]. Higher concentration of TNF-α in African child can increase NO level that interferes with synaptic transmission, diffuse across the BBB to the brain, and lead to coma [24]. While in adult patients, increased levels of cytokine are related to more severe complications. Although plasma concentrations of cytokine TNF-α, interleukin (IL)-6, and IL-10 were higher in Vietnamese adults who died with severe malaria, these increases were not associated with CM [25]. In children who develop CM followed by fever, seizures most commonly occur after suddenly developed coma; while in adults, seizure is associated with gradually developed coma [23]. The risk of seizure is increased with parasitemia and related to intracranial pressure [26]. Recent study using mouse model infected with *P. berghei* ANKA showed that IL-6 and transforming growth factor (TGF)-β are involved in immune regulation of dendritic cells, regulatory T cells, and Th17 cells during experimental CM [27]. In addition, erythropoietin levels increase malaria severity degree in patients infected with *P. falciparum* in Sub-Saharan countries [28].

African Trypanosomiasis

Human African trypanosomiasis (HAT), also known as sleeping sickness in humans, is a significant cause of morbidity and mortality in sub-Saharan Africa caused by parasitic *T. brucei* [29]. *T. brucei* has been grouped into three subspecies: *T. b. brucei*, *T. b. gambiense*, and *T. b. rhodesiense*. Only two of them are human infective, e.g., *T. b. gambiense* causes chronic form of HAT in west and central Africa and lasts for several years, *T. b. rhodesiense* causes acute form of infection in east and southern Africa and lasts from weeks to months of infection [30].

Clinical Symptoms of African Trypanosomiasis

Infection of trypanosomes can be categorized into 3 stages. At the beginning, a chancre filled with *T. brucei* parasites and characterized by erythema, tenderness, heat, and edema, often develops at the site of the bite of infected tsetse fly within a week or so. After chancre formation, the hemolymphatic stage occurs due to a spread of the parasites through the bloodstream and lymphatic into various organs such as liver, spleen, endocrine glands, and heart [31].

Meningoencephalitis stage is the most severe stage that may occur at any time from weeks to years after the initial infection from the invasion of parasites across the BBB into the CNS. Sleep disturbance has also been observed in the patients. Encephalitis lethargica related to 'sleeping sickness' is characterized by acute or sub acute clinical manifestations of one of the three types: somnolent-ophthalmoplegic, hyperkinetic, or amyostatic-akinetic [32].

Pathogenic Mechanism of African Trypanosomiasis

The early stage of HAT is characterized by an elevation in pro-inflammatory cytokines with a switch to a counter-inflammatory response in late stage infection [33]. When *T. brucei* parasite entershuman host, it secretes enzyme cysteine proteases that may promote the parasites to go through the BBB to the brain. Type 1 helper T cells (Th1) response of pro-inflammatory cytokines such as interferon-gamma (IFN-γ) and TNF-α is elicited in the infected host for killing intracellular parasites. The brain pathological findings consisting of lymphocytes, plasma cells, and macrophages occur in the leptomeninges [34]. These processes can lead to somnolence, coma, and even death if untreated. Elevated IL-10 were detected in the plasma and cerebrospinal fluid (CSF) in both early-and late-stage of *T. b. rhodesiense* infection [35]. Elevations of CSF IL-10 level as well as levels of IL-6 and IL-8 in patients-infected with *T. b. gambiense* have also occurred in the late-stage infection [36]. Increased CSF prostaglandin D2 levels in patients with CNS African trypanosomiasis may be related to the marked somnolence, while increased blood and CSF endotoxin levels may contribute to the CNS pathology [36,37].

Activated astrocytes and macrophages were found in the perivascular cuffs and adjacent parenchyma and pathognomonic morular, modified plasma cells containing eosinophilic inclusions comprising IgM were found in the white matter of late-stage HAT patients [34]. Two high-density lipoprotein (HDL) components have been reported, one is apolipoprotein L-I (apo L-I), a human HDL component, able to kill *T. b. brucei,* and another is haptoglobin-related protein (Hpr), acts as an additional toxin required for full trypanolytic activity of normal human serum; in which apo L-I is probably the sole trypanolytic factor of human blood [38]. *T. b. gambiense* and *T. b. rhodesiense* are surrounded by surface coat composed of a variant surface glycoprotein that protects them from human plasma lytic factors [39]. These glycoproteins are recognized by the host's immune system when infection occurs, which then starts producing IgM and IgG antibodies to neutralize the corresponding trypanosomes and decrease parasitemia [40]. At peak parasitemia, the parasite releases variant-specific surface glycoprotein into circulation to induce inflammatory responses [41]. Thus, the host's immune system cannot eliminate the parasites from the body [42]. Previous studies reported that antibody production of trypanosome specific IgM and IgG in the CSF of late-stage patients was the main mechanism in controlling parasitemia [43]. However, using murine *T. b. brucei* model of B-cell (micro MT) and IgM-deficient mice to investigate the role of B cells and IgM antibodies in parasitemia control, it demonstrated that B cells play a critical role in periodic peak parasitemia clearance while IgM antibodies only play a limited role during the infection [44].

Toxoplasmic Encephalitis (TE)

T. gondii is one of the world's most common parasites infecting most genera of warm-blooded animals, including humans, as it infects 30%–50% of the world human population. TE, an infectious disease causing inflammation of the brain, is caused by the obligate apicomplexan intracellular protozoan *T. gondii* [45]. Undercooked meat such as pork, lamb, and wild game meat, and raw fruits and vegetables contaminated with cat feces are the major sources of human *T. gondii* infection [46]. Vertical transmission of the parasite is also a potential way of infection for the fetus and can lead to miscarriage or congenital toxoplasmosis [47]. A majority of infected individuals is usually clinically asymptomatic; however, TE can have serious symptoms and even be fatal in immune-compromised individuals [48].

Clinical Symptoms of TE

The majority of infections persist asymptomatically for the lifetime of the host; while toxoplasmosis is life threatening in immunocompromised patients such as AIDS, organ transplant, and cancer patients. Symptomatic infection with the parasite can lead to 1) cervical lymphadenopathy, headache, fever, sore throat, myalgia, splenomegaly, and possibly brief erythematous rash; 2) retinochoroiditis, and 3) atypical pneumonia, myocarditis, meningoencephalitis or the CNS involvement, and even death [45]. It has been reported that the incidence of severe primary toxoplasmosis in immunocompetent adults in French Guiana with visceral involvement, especially lung involvement. The unusual form of toxoplasmosis may be associated with atypical genotypes of *T. gondii* [49]. Acute infection of toxoplasmosis during pregnancy is detrimental to the developing fetus, and may result in devastating neurologic impairment [50], such as neurological and ocular diseases and may also lead to late sequelae in the life of the infected newborn [51].

Pathogenic Mechanism of TE

T. gondii is able to invade a wide variety of host cells. *T. gondii* can invade and multiply inside any nucleated cell type including epithelial cells and blood leukocytes [52]. During invasion, the proteins called micronemes, dense granules, and rhoptries (ROPs) are secreted from parasite organelles into the host cell [53].The calcium-dependent secretion of adhesions from micronemes such as the microneme protein MIC2 is required to promote the parasite reorientation and attachment to the host cell membrane. The secretion of proteins from the ROPs also helps to form the nascent parasitophorous vacuole membrane (PVM) [54]. Besides ROP proteins, dense granular proteins also contribute to the formation of the PVM following invasion. Some of these dense granule proteins may be involved in the development of intravacuolar membranous network, and they may also be key elements of the cyst formation [55].

Reactivation of TE has been described in patients characterized by impaired cell-mediated immunity [56]. TE/AIDS patients produce low Th1 response (IFN-γ) andTh2 response (IL-10) but high TNF-α level, suggesting a high inflammatory response triggered by *T. gondii* [57]. CSF and serum assessment revealed elevations of both anti-toxoplasma IgM and IgG in TE patients [58]. T cells and IFN-γ are essential for prevention of reactivation of cerebral infection with *T. gondii* [59]. $CD4^+$ and $CD8^+$ T cells are required for protection against TE, and $CD8^+$ T cells play a dominant role in protection during chronic toxoplasmosis [60]. Vascular cell adhesion protein-1/α4β1 integrin interaction is vital for prompt recruitment of both $CD4^+$ and $CD8^+$ T cells into the brain and stimulation of IFN-γ-mediated protective immune responses to prevent reactivation of cerebral infection with

the parasite [61]. IFN-γ, produced by brain-resident cells such as microglia, is essential for upregulating both the protective innate and T cell-mediated immune responses to control cerebral *T. gondii* infection [62]. It has been demonstrated that increased NO level may contribute to neuropathology related with TE in mouse model [63]. TGF-β signaling in astrocytes is activated during TE, and increased immune cell infiltration and neuronal injury were observed once astrocytic TGF-β signaling be inhibited [64]. Significant increased TLR11 protein and gene expressions in astrocytes, microglia/macrophages, and neurons were induced during *T. gondii* infection in experimental animal model [65].

Conclusion

Overall, encephalitis caused by parasites remains a serious global public health threat and causes substantial morbidity and mortality in the world. Malaria and human African trypanosomiasis is represent the two major tropical vector-transmitted protozoan infections that can involve the CNS, while *T. gondii* eventually leads to persistent infection characterized by the presence of tissue cysts in the brain of the host, and reactivation of these cysts can lead to TE in the immunocompromised host. Since brain parasitic infections are potentially treatable, choosing the appropriate treatments for the infections are of great importance. In this article, we highlight the common immune-mediated mechanisms leading to brain involvement by *P. falciparum*, *T. brucei*, and *T. gondii*. Further efforts are needed for a better understanding of the pathogenesis of the parasitic encephalitis.

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