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Review

A proposed cascade of vascular events leading to granulomatous amoebic encephalitis

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ABSTRACT

Granulomatous amoebic encephalitis due to *Acanthamoeba* is a chronic disease that almost always results in death. Hematogenous spread is a pre-requisite followed by amoebae invasion of the blood-brain barrier to enter the central nervous system. Given the systemic nature of this infection, a significant latent period of several months before the appearance of clinical manifestations is puzzling. Based on reported cases, here we propose pathogenetic mechanisms that explain the above described latency of the disease.

1. Introduction

Acanthamoeba spp. and *Balamuthia mandrillaris* are known to cause fatal granulomatous amoebic encephalitis (GAE), which is accompanied by common signs and symptoms (Table 1) in neurological involvement that almost always results in death, as evidenced by greater than 90% mortality rate [1,2]. GAE is different from other commonly occurring neurological granulomatous diseases (e.g., fungal and tuberculous), in that, it terminates the life of the host ahead of the typical gliotic/fibrotic changes that appear as the end result of any granulomatous lesion [3]. Most patients suffer from seizures, and focal neurological deficits, accompanied by loss of consciousness, cerebral edema with intracranial hypertension, ultimately leading to brain death [4]. Several lines of evidence suggest that amoebae invade lungs/skin and gain access to the intravascular space, followed by haematogenous spread, leading to interactions with the blood-brain barrier and finally invading the central nervous system (CNS) to induce disease [1,2,4]. Following acquisition of the infectious agent, the factors that play important roles in amoebal invasion of the CNS, include its ability to tolerate physiological conditions (temperature, osmotic shock, pH variations), adherence properties (mannose-binding protein), catalytic products (proteolytic activities), and immune evasion mechanisms [1,5]. The biopsy and/or autopsy finding of GAE patients shows perivascular cuffing and it is considered as a chronic disease, lasting from 6 months upto two years [2,4].

Despite recent advances in our understanding of the development of the disease, it is unclear why systemic manifestations appear after months of latency. This is in contrast to other blood-borne neuropathogens, such as meningitis-causing bacteria, which spread systemically leading to the CNS invasion within a short duration of time. Based on the histopathological findings, here we propose two possible routes for CNS invasion by *Acanthamoeba*, including the transendothelial route and the rete vasorum or a combination of both; this may explain the significant latent period of several months to years before the appearance of neurological manifestations. In this commentary we will try to answer these questions with rationale and logic that could be tested using *in vivo* model of the infection, as well as advanced imaging procedures.

2. The trans-endothelial route

In order to access the vessel wall, trophozoites are required to come in contact with the endothelial glycocalyx. Cerebral circulation, because of its anti-gravity blood flow in the deeper cerebral tissue, as well as torturosous blood vessels appear to be an ideal site

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Table 1
Syndromic manifestation of neurological involvement in amoebic encephalitis caused by free-living amoeba. The deficits depend upon the area of the brain involved (data source: [4]).

- Headache
- Mental status abnormalities
- Seizures
- Meningism
- Irritability blurred vision
- Nausea and vomiting
- Hemiparesis
- Cranial nerve palsies Perineural infiltrates
- Gait ataxia
- Diplopia Irritation
- Photophobia
- Sleep distrubances
- Anorexia
- Babinski's sign
- Kernig's sign

for such contacts. These sites are well known for platelet contacts and therefore development of thrombi and stroke in hypertensive and vasculitis predisposed individuals [6]. Notably, the occurrence of GAE in patients with vasculitis-associated diseases like systemic lupus erthromatosis and *diabetes mellitus* [7,18] also explains our endothelial injury rationale as a predisposing factor for amoeba and endothelial interaction. Following initial transient contact mediated by mannose-binding protein (MBP), and laminin-binding protein (LBP) reported previously [8,9], *Acanthamoeba* exhibits close tight adherence to the endothelial cells. In this regards, several adhesion molecules have been identified on endothelial cells, including P-selectin/L-selectin and intercellular adhesion molecule-1 (ICAM-1, or CD54) that are known to bind to CD11a-CD11b adhesin [10]. Human leukocytic alpha integrins, CD11a and CD11b [11] are known to promote tight adherence prior to trans-endothelial migration and subsequent entry into the blood vessel wall. Bioinformatic analysis revealed a cell surface alpha integrin homolog on *Acanthamoeba* spp. termed integrin-α FG-GAP repeat-containing protein (Accession:XP_004338902.1). The protein sequence FASTA blast of which on human proteomics database revealed a homologous alpha integrin (Accession: EF560727.1 – E-Value = 2e – 09), validated similar interactions of amoeba with the injured endothelium as likely route for their migration across the vascular endothelium and entry into the blood vessel wall. It is plausible that the aftermath of amoebae adherence to endothelial cells would result in further endothelial injury to gain entry into the blood vessel wall, i.e., tunica media. These findings would support the notion that endothelial injury is a possible route for amoebae entry into the tunica media (Fig. 1), and the explanation of the etiology for the aforementioned thrombi, found in patient biopsies showing perivascular cuffing. Once within the vessel wall, the next obstacle for these pathogens is to counter leukocyte attack that attempt to contain them by formation of granuloma. The finding of a glycocalyx denuded endothelium, a combating effect by leukocytes and granulomatous walling-off attempts by the host immune system [12–14], may be the major reasons for the transit time that is taken for a full blown GAE to occur. The perivascular cuffs and the subsequent granulomas that prevent the access of amoebae may explain significant delay observed in syndromic manifestation of GAE after acquisition of the infectious agent. In other chronic granulomatous lesions of tissues like lungs, it is common to find a delay of several weeks to months before the onset of clinical signs and symptoms after acquiring the infectious agent. Tuberculosis and fungi are classic examples of latter infectious diseases that invite granuloma formation and show a delayed clinical onset even in immunocompromised individuals [3]. The ability of amoebae to overcome these immune-mediated attempts, are likely attributed to extracellular toxins, amoeboid movement, cytotoxic enzymes, metalloproteinases, pore-forming toxins, etc. that enable amoebae to breach the granuloma to eventually reach and damage the neurones in the brain tissue [1,2,4,14]. Unlike tuberculosis bacilli that do not have any exotoxins, these protist pathogens are well

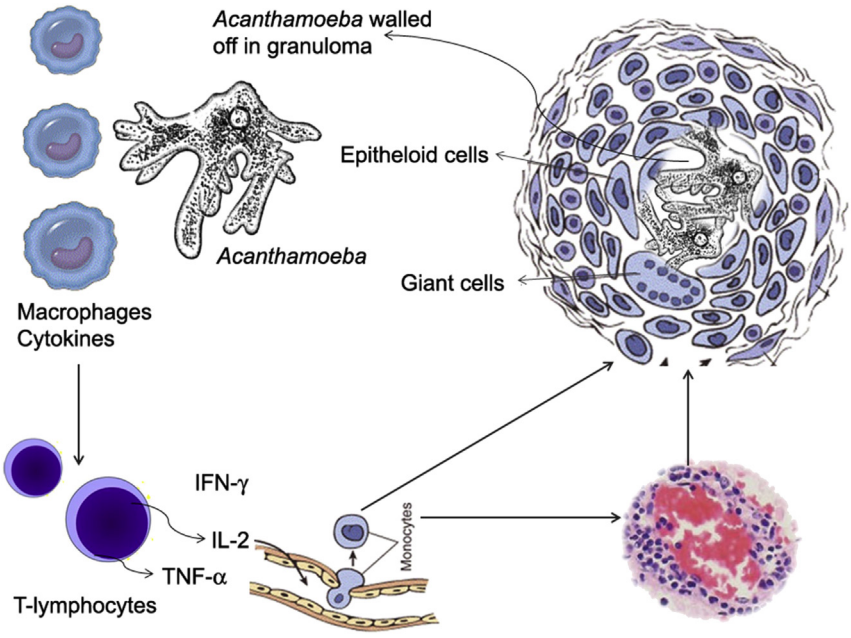

Fig. 1. The tissue macrophages on being unable to phagocytose *Acanthamoeba* and *Balamuthis* spp., produce monokines to recruit lymphocytes to the site of amoebal invasion. The CD4+ve lymphocytes recruit circulating monocytes to the site of the amoebal presence and convert them to epitheliod cells and giant cells by producing lymphokines. After a initial perivascular cuffing (bottom right) these lesion over a period of weeks convert into granuloma (top right). The typical features of granuloma are shown here, apparently attempting top wall-off the trophozoites.