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Infectious Diseases of the Nervous System and Their Impact in Developing Countries

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Infectious diseases of the nervous system in the developing world have been relatively neglected. This is paradoxical because neurotropic pathogens are common and contribute significantly to human suffering and disease burden in these regions. Clearly, living with a neurological handicap and/or cognitive dysfunction may have a strong negative impact on socioeconomic development. Here, we briefly describe a few examples of such infections causing severe diseases that result in the loss of motor-sensory function (cerebral malaria, viral encephalitis), alterations of cognition/behavior (AIDS), or sleep perturbations (African trypanosomiasis). Importantly, there is an opportunity to interfere with infection because the central nervous system (CNS) is not usually the primary site for pathogen infection.

Cerebral Malaria

Cerebral malaria (CM) is one of the most severe complications of Plasmodium falciparum malaria. It is most common in young children living in malaria-endemic sub-Saharan Africa where CM incidence is 1–12 cases/1,000 children per year and the mortality rate can be as high as 22%, as described recently in a large cohort of Kenyan children (<14 years old) [1]. Malaria was found to be associated with neurological involvement on admission in nearly half of the patients (with an incidence of 47.6%), and their mortality was increased when compared to malaria patients without neurological signs. The main clinical features consist of seizures often preceding deep coma resulting from cerebral edema, microhemorrhages, and ischemia. Erythrocytes containing malaria parasites accumulate in brain microvessels where leukocytes and platelets are also found.

The multi-factorial complexity of this syndrome has been related to the parasite’s release of glycosylphosphatidyl-inositol, which binds to pattern recognition receptors, triggering an inflammatory response and cytokine/chemokine release. TNFα upregulates the endothelial intercellular adhesion molecule ICAM, enhancing binding of parasitized erythrocytes to vascular endothelia with eventual disruption of the blood-brain barrier (BBB) [2]. This may result in activation of microglial cells and astrocytes, demyelination, and/or neuronal injury [3]. Important insights have come from clinical studies, post-mortem analyses of brains from CM victims, in vitro studies of the adherence of parasitized erythrocytes to brain endothelial cells, and genetic studies of susceptibility and resistance determinants in mice and humans [3]. Balanced views on other aspects of CM pathogenesis and pathophysiology, including metabolic acidosis and capillary dysfunction, have been discussed by Idro et al. [1], who proposed renaming CM as “malaria with neurological involvement”, which leads to long-term neurological sequelae and/or behavioral problems in 24% of cases, imposing a major burden on African children.

Although CM is associated with a dramatic activation of brain endothelial cells, with increased expression of ICAM (see [2,3] for review), remarkably it does not exhibit perivascular infiltrates, and no intravascular migration of leucocytes occurs. Thus, in CM, inflammation and immune-mediated events remain essential, in contrast to other neuroinflammatory disorders, such as multiple sclerosis, which is characterized by perivascular infiltrates and no intravascular sequestration of leucocytes. Furthermore, the Plasmodium-infected erythrocytes also remain intravascular, in contrast to the direct CNS invasion by other pathogens, such as in toxoplasmosis. Consequently, unless marked hemorrhages occur, there is a limited involvement of parasites or of leucocytes within the CNS parenchyma itself. It is not possible, however, to draw conclusions about a lack of inflammatory pathogenesis, because, most if not all, brain pathology is mediated by intravascular inflammatory events. Concerted interdisciplinary actions are needed to reach a better understanding of CM pathogenesis and the intricate roles of parasite-derived toxins, proinflammatory cytokines, and adhesion molecules. The discovery of increased numbers of endothelial cell membrane-derived microparticles in the circulation during acute CM raises the question of their pathogenic role, as suggested by disease protection in mice lacking one of the genes controlling microparticle formation [4].

Deciphering the precise host immune responses associated with micro-environmental alterations leading to CM is crucial for devising novel therapeutic strategies. Treatment compounds need to be simple, safe, and effective.


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Effects of Trypanosoma cruzi infection on brain function in HIV infection

The neurobiological basis of these conditions is not due to direct HIV infection of neurons, but to synaptodendritic alterations called “beading” [14]. Cortical motoneurons and interneurons that show these alterations may eventually die of apoptosis.

In sub-Saharan Africa, where AIDS is prevalent, HAD incidence was studied recently using an accurate, cross-cultural HAD scale [15]. In Uganda, where clades D and A dominate, 31% of AIDS patients develop HAD, which can affect verbal memory, fine and gross motor performances, psychomotor speed, and executive functions. Affected individuals have a higher rate of unemployment than controls and show poor performance in daily family life. In contrast, in Ethiopia where HIV clade C dominates, only minor cognitive alterations were reported in AIDS patients. The lesser impact of HIV on cognitive functions in this case could be explained by the poor ability of HIV clade C isolates to grow in macrophages, a characteristic of neurotropic strains.

Some envelope glycoprotein variants (named N283) are more frequently isolated from infected brains than from other organs [16]. These variants were likely selected by their ability to bind to low levels of the HIV receptor CD4 and coreceptor CCR5 on perivascular macrophages and microglia residing in the CNS. Viral replication in these target cells results in the formation of multinucleated cells. Such giant cells also produce virus that will further spread and persist in the brain where HIV protease inhibitors have limited accessibility. Clearing such a viral reservoir would require specific inhibitors for neurotropic variants that can cross the BBB [17].

More epidemiological studies of HAD and HAND should determine the impact of HIV infection on brain function in different regions of sub-Saharan Africa. To decrease the negative impact of these syndromes on patient cognitive behavior and improve societal acceptance of individuals with HAD or HAND, one needs to isolate and characterize neurotropic viral subtypes from the cerebrospinal fluid early in AIDS. This might allow designing ways to block HIV entry into the CNS.

Emerging Infectious Diseases of the CNS

Viral encephalitis is emerging or re-emerging as an important cause of human disease due to increased geographic range...
Emerging viruses, half of which cause efficiently transmitted, are associated with that are more virulent for humans or more efficiently transmitted, are associated with emerging viruses, half of which cause serious neurological diseases [20].

Arthropod-borne viruses have been restricted in range geographically by the availability of their vertebrate and vertebrate hosts. However, modern transportation has introduced vectors that efficiently transmit arboviruses into new areas (e.g., the Asian tiger mosquito Aedes albopictus into North America and Europe). In many areas, pre-existing populations of competent vectors set the stage for successful establishment of viruses in new regions. Recent examples are the introduction of West Nile virus into North America, where susceptible vectors and hosts were abundant and rapid spread across the continent has resulted in more than 11,000 cases of CNS disease, and the arrival of a strain of Chikungunya virus adapted to Aedes albopictus in southern Europe. West Nile virus has the widest distribution of all flaviviruses, its range spreading to Africa, North, Central, and South America, West Asia, Europe, the Middle East, and Australia [18].

Japanese encephalitis and Rift Valley fever viruses could easily follow the same pattern.

Bats are increasingly recognized as important hosts for a number of zoonoses that cause CNS infection (e.g., lyssaviruses, hantaviruses, coronaviruses, and filoviruses). Disruption of the environment with changing agricultural practices has increased the likelihood that these viruses will be transmitted to humans, as suggested by Nipah and Hendra virus outbreaks. New outbreaks of Nipah encephalitis, nine of which have occurred in Bangladesh since 2001, resulting in the death of 40%–75% of infected people, indicate human-to-human as well as bat-to-human transmission [21].

There are currently no treatments available for these viral CNS diseases. Development of antiviral agents may be useful, but treatment at the time of symptoms may not be effective. Vaccines are likely to be the most effective interventions and are available or in development for many of these viruses (viz., Japanese encephalitis, tick-borne encephalitis, and West Nile); however, to be effectively utilized, spread of the virus must be monitored and disease outbreaks anticipated.

**Perspectives**

There is an urgent need for continued surveillance and identification of viruses in vertebrate and invertebrate hosts to anticipate the introduction and spread of new and old agents. A better understanding of the mechanisms of entry into the CNS, of neuronal damage, the immune response to virus infection, and prevention of CNS infection will guide the development of appropriate interventions.

The questions raised here are part of a broader field of investigations on a dozen neurotropic pathogens that were discussed at a September 2008 conference in Paris, “Infections of the Nervous System: Pathogenesis and World Impact.” This conference has addressed the current gaps in knowledge and set the stage to establish an agenda for confronting this group of diseases in the coming years. Abstracts have been published in *BMC Proceedings* ([22]; http://www.biomedcentral.com/1753-6561/2/issue=S1). We need to increase the awareness of the world’s leading institutions on the impact and challenges in this field and to foster new research and training programs that will trigger new ideas to study the mechanisms of pathogen spreading and neural cell dysfunction in close contact with clinical research and surveillance, diagnosis, and treatment of infectious neurological diseases. Progress will depend on the development of a systemic approach based on cross-fertilization between clinicians studying disease mechanisms and scientists working on the life cycle and molecular makeup of neurotropic infectious agents and their vectors; between immunologists studying innate and adaptive immune responses to neurotropic pathogens and cell biologists investigating pathogen interactions with the BBB and neural cells; and between leaders in new technologies for diagnosis and therapies and medical anthropologists.

**References**