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Review

Epilepsy in the tropics: Emerging etiologies

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ABSTRACT

Epilepsy is considered by the World Health Organization a public health priority with more than 50 million human beings affected by the disease. More than 80% of persons with epilepsy live in low and middle income countries and most of them in tropical areas. Several emerging, re-emerging and neglected diseases are symptomatic etiologies that jointly contribute to the enormous global burden of epilepsy. Besides the clinical strengths to reduce diagnostic and treatment gaps, other strategies in social, economic, cultural, educational and health policies are needed to prevent and treat appropriately vulnerable and affected persons with epilepsy. From the public health point of view, several of those strategies could be more effective in reducing the incidence and burden of the disease than the clinical approach of diagnosis and treatment. Special attention has to be given to stigma reduction and promotion of human rights. Several aspects mentioned in this abstract slip away the scope of the article, but it is a remainder to approach epilepsy in an inter- and transdisciplinary manner, an integral and pertinent approach needed and requested in tropical counties. The article focuses only on emergent and re-emergent etiologies of epilepsy in the tropics like malaria, HIV, neurocysticercosis, viral encephalitis and traumatic brain injury.

1. Introduction

1.1. Epidemiology

Malaria is the world's most common fatal parasitic disease and is endemic in Africa, Asia, tropical America, and subtropicalareas of the eastern Mediterranean. Almost half of the world's population-approximately 3.2 billion people, are at risk of malaria [1].

The majority (90% of all malarial deaths), are mostly among children under 5 years of age in sub-Saharan Africa. In 2015, there were an estimated 438,000 malaria deaths [1]. Severe malaria, a complex multi-system disorder is predominantly caused by *Plasmodium falciparum*. Cerebral malaria (CM), an acute non-traumatic encephalopathy remains one of the most serious complications of *P. falciparum*. Malaria with young nonimmunized adults traveling from nonendemic areas and children below the age of 5 years are most vulnerable. Pregnant women are equally at risk due to lowered immunity during pregnancy.

1.2. Clinical features

Symptomatic seizures are seen not only in CM but also in uncomplicated benign forms of malaria [2]. In a Kenyan hospital, Malaria was responsible for 69% of the causes of seizures in the children admitted on the ward [3]. The frequency of seizures as a presenting symptom in a malarial episode varies from 22% in South and South East Asia to 80% in Africa [4]. Seizures usually occur in acute phase of malaria but may also occur in the later part of the illness. Acute symptomatic seizures are often focal, usually repetitive and prolonged with or without secondary generalization, but may be generalized/subtle or purely electrographic seizures [3]. Status epilepticus is common in children and often associated raised intracranial pressure, with signs of brain oedema on neuroimaging [5].

Epilepsy is a recognized neurological sequelae of CM [6]. The risk factors for epilepsy in children with CM are hyperthermia, presence of acute seizures and family history of epilepsy [7,8]. Findings from a study among children of 6–9 years of age admitted to a district hospital in Kenya over an 8-year period, showed an increased prevalence of epilepsy in children with CM and malaria with complicated seizures compared to unexposed children [9]. Another study conducted among children, aged 0 months to

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15 years in Gabon, revealed that the risk of developing epilepsy was 3.9 (95%CI: 1.7–8.9; $p < 0.001$) times greater among those with prior exposure to CM than among the unexposed [8]. A hospital based study conducted in Uganda also showed that more than half (52%) of the CM survivors developed epilepsy [10].

Generalized tonic–clonic seizures, as well as focal seizures have been recorded in the epilepsy episodes of CM survivors [9]. It has been demonstrated that the focal seizures relate to the epileptic focus (established by seizure semiology, EEG, and neuroimaging) and match the respective focal brain regions involved with status epilepticus or the recurrent seizures in the course of the acute CM episode [7].

1.3. Pathogenesis

The mechanisms that stimulate the process of epileptogenesis following the acute CM episode are unclear. However several theories have been implicated as contributing factors. The Durck's malaria granuloma formed by an astroglial reaction following brain damage from blood vessels plugged with parasitized red blood cells may act as epileptogenic foci, giving rise to chronic epileptic seizures. Neurotoxic effects in the form of increased concentration of quinolinic acid that creates excitotoxic mechanisms; presence of higher levels of *voltage gated calcium channel (VGCC)* antibodies in children with malaria and possible underlying genetic mechanisms have also been suggested [11,12].

1.4. Management

Timely and effective management of falciparum malaria associated with seizures will impact on a more favorable outcome in severe malaria. It has been shown that benzodiazepines are not as effective in malarial associated seizures compared to other conditions due to their suppression of the response of the γ-aminobutyric acid receptors. Nevertheless, benzodiazepines are the mainstay in the management of acute seizures in malaria.Prolonged seizures can be managed with phenobarbital or phenytoin [13–16].

2. Human immunodeficiency virus infection

2.1. Epidemiology

The Human immunodeficiency (HIV) virus has affected approximately 78 million persons since the start of the epidemic, with over half of all new HIV infections worldwide and an estimated 70% of the HIV-infected persons residing in the world's most affected region, eastern and southern Africa. With the recent extraordinary scaling up of HIV treatment in several settings, an increasing number of persons living with HIV are accessing antiretroviral (ARV) medications, estimated at 17 million people, as of end December 2015. The increased access to ARVs, coupled with early linkage to specialist care and appropriate prophylaxis for opportunistic infections, has led to persons with HIV living longer on effective treatment. Consequently, this situation has steered the rising challenge of managing the increased incidence of non-communicable diseases in HIV patients, amongst which include neurological disorders such as seizures [17,18].

2.2. Pathogenesis

The predominant pathway to HIV-1 neuronal injury is indirect through release of macrophage, microglial and astrocyte toxins, although direct injury by viral proteins might also contribute. These toxins overstimulate neurons, resulting in the formation of free radicals and excitotoxicity, and this process can lead to seizures. In a study of 100 cases of new-onset seizures in HIV-infected patients, there was no definite etiology for seizures despite extensive neurologic, radiologic, and laboratory evaluation in 23% of patients [19].

The epidemiology of seizures in patients with HIV-1 infection can occur at any disease stage, with their occurrence dependent on the patient's immune status and with several potential seizure-causing processes that may operate concurrently. Apart from free radical injury, other mechanisms in which seizures may occur include: reactivation of previously acquired organisms such as tuberculous meningitis or cerebral toxoplasmosis; the development of AIDS-related cancers, like CNS lymphoma; presence of the disorder progressive multifocal leukoencephalopathy; infections such as brain abscesses, encephalitis and meningitis especially cryptococcal meningitis; metabolic disturbances including hyponatremia, hypomagnesemia, hypocalcemia associated with hepatic or renal failure; HIV encephalopathy; medication side effects especially for those on multiple medications for other co-existing illnesses in addition to their ARVs; and presence of cerebrovascular disease [20–23].

2.3. Clinical features

Seizures as the presenting clinical symptom of HIV infection have been reported in 3–17% of cases. Generalized seizures are seen in the majority of the HIV patients; with focal seizures observed in about 25–30% [23]. Whereas epidemiologic data on the rates of seizure recurrence in HIV infected patients is lacking, a clinical study reported 65% of cases having repeat seizures [24]. Furthermore, there is a risk of subsequent development of epilepsy with presence of intravenous drug abuse, a history of previous head trauma or positive family history of epilepsy increasing the risk [21]. Convulsive status epilepticus has been reported in 8–18% of cases. Electroencephalographic findings are usually non-specific, with diffuse slowing being the most common abnormal pattern and associated with more advanced HIV infection [19,21,24,25].

2.4. Management

The standard clinical guidelines for critical acute seizure termination using benzodiazepines are recommended, while those patients at risk for the development of status epilepticus, the standard status epilepticus protocol should be followed. A detailed history and thorough investigation to identify the possible aetiology and institute the appropriate therapy should be made. If chronic antiepileptic drug (AED) therapy is to be administered, caution should be employed to understand each AEDs pharmacokinetic profile so as to limit the interactions between AEDs and ARVs which may result in breakthrough seizures, virologic failure, or drug toxicity [22,26]. The older generation CYP450 enzyme inducing AEDs such as phenobarbital, phenytoin and carbamazepine should be avoided in people on ARV regimens that include protease inhibitors or nonnucleoside reverse transcriptase inhibitors [26]. Levetiracetam if accessible, is a promising AED in HIV infected patients owing to the simplicity of its administration, negligible drug interactions, good side effect profile and broad spectrum activity [27]. Other promising new AEDs are gabapentin, pregabalin and lacosamide. All these new AEDs though FDA-approved as adjunctive therapy, can be used as monotherapy in the HIV patients. In the absence of newer AEDs, valproic acid may be a possible alternative despite the in vitro association with increased HIV viral replication and risk of hepatic failure when used concurrently with ARVs. This finding has however been negated in in vivo studies [28].

3. Neurocysticercosis

3.1. Epidemiology

Neurocysticercosis is the infection of the central nervous system caused by the larval form of *Taenia solium*. The World Health Organization considers cysticercosis to be the most common preventable cause of epilepsy. In developing tropical countries it may account for one-third of seizure disorders with an estimated 2 million of affected persons. Neurocysticercosis accounts for about 50,000 deaths per year. Poor sanitation policies and low educational opportunities contribute to permanent burden of the disease in low and middle income countries. Political and economic instability, civil wars, discrimination, pursuit and migration have expanded the disease into developed countries. Seroprevalence of T. solium cysticercosis ranged from 3,7% to 24% in Latin America, 2% to 13% in Asia and 6% to 22% in Africa. Humans get infected by eating contaminated food with feces containing eggs of T. solium or through autoinfection. Eggs madurate to oncospheres that cross the intestinal wall migrating to muscle, brain, liver, retinae and other tissues, where they develop into cysticeri [29,30].

3.2. Clinical features

Up to 80% of symptomatic neurocysticercosis have seizures that have the semiology of focal or secondarily generalized tonic clonic seizures. Clinical seizures appear as an acute manifestation of active or degenerating cysts, but can also be the symptoms of established epilepsy of calcified lesions in the brain. Other neurological manifestations are headache, focal neurological signs, raised intracranial pressure, psychiatric and behavioral changes, gait disturbances and dementia [31].

Epilepsy due neurocysticercosis should always be kept in mind in persons living or coming from endemic areas. Confirmation include neuroimaging and serological studies. Cerebral lesions are classified as active, transitional and inactive types and can appear as a single nodular lesion or as uncountable lesions. Further support for the diagnosis of neurocysticercosis is the different evolutionary stages of the lesions in the brain. Limited access to neuroimaging studies in developing countries frequently defer the diagnosis of neurocysticercosis.

Specific serologic studies like enzyme linked immunoelectrotransfer blot assay (EITB) guide which patient should be derived to neuroimaging studies. Its low sensitivity for single parenchymal lesion leads to false positive results and makes diagnosis harder in India where the variant of single nodule cysticercus is more common than in other parts of the world. Other serologic studies with antibodies against *T. solium* show exposure to the parasite and not necessarily tissue involvement including the brain. New diagnostic criteria for neurocysticercosis have been proposed recently [31,32].

3.3. Management

Symptomatic treatment should not be delayed, in the situation of acute seizures benzodiazepines are used, and in epilepsy first line antiepileptic drugs should be used. Anti-inflammatory drugs are indicated for subaracnoid, intraventricular and multiple parenchymal cysts that can cause inflammation due to natural degeneration or anti-parasitic drug reaction. Steroids have shown seizure reduction due to single nodule cysts in Asia. Antiparasitic drugs like albendazole and praziquantel are used for active forms of neurocysticercosis in patients with stable symptoms and without a high risk of increased intracranial pressure [33,34]. Improved sanitation, increased awareness in the general population, qualified pig farming and marketing, avoidance of irrigation with contaminated water and availability of anti-parasitic drugs will decrease the burden of neurocysticerocosis.

4. Zika

Zika outbreak has caught public attention in the last 2 years in the Americas. On February 2015 an outbreak of an exanthematic disease in Northeastern Brasil was confirmed to be related to Zika virus, and its fast spreading followed during the next months to Colombia, Central America and nearly all South American countries. Zika virus is an arthropod-borne virus (arbovirus) in the genus *Flavivirus* and the family *Flaviviridae*. Vector transmission occurs through *Ae. aegypti* and *Ae. albopictus*, and non-vector transmissions have been described via sexual intercourse, laboratory contamination, materno-fetal transmission and transfusion. In late December 2015, the estimated number of suspected cases of ZIKV infection ranged from 440,000 to 1,300,000 and in February 2016 and in January 2016 an estimate of about 14,000 cases was reported in Colombia. The Zika epidemics in the Americas are accompanied by unexpectedly neurological manifestations with microcephaly and Guillain–Barré syndrome. In January 2016 Brazil has reported 3893 newborn babies with microcephaly and the WHO declared a global health emergency. Diagnosis is made under clinical suspicion with serological tests. Vaccination studies are under research and prevention measures include vector control and avoidance of mosquito bites. Epilepsy is expected to appear with the raising birth defects of newborn babies. Modeling Zika virus infection during pregnancy is also underway. Epidemiologic concern exists of a further vector spreading of Zika and of the risk of worldwide future affected fetuses due to non vector but sexually transmitted virus after the Olympic Games in Rio de Janeiro [35–38].

5. Tuberculous meningitis

5.1. Epidemiology

Tuberculosis continues to be an important infection worldwide, with 8.8 million new cases in 2005, 84% in Asia and Sub-Sahara Africa. About 1% of tuberculosis involve the central nervous system. In many of the neurology or infectious disease units in the developing world, tuberculous meningitis (TBM) remains to be a common and important clinical problem. TBM has high mortality and morbidity [39]. At the University Malaya Medical Centre, which is a teaching hospital in Kuala Lumpur—Malaysia, the mortality rate is about a third, and another third survive with significant morbidity.

5.2. Pathogenesis

The pathology consists of basal leptomeningeal inflammation, tuberculoma which are usually multiple and small but can also be single and large; arteritis and infarct particularly at the areas supplied by the perforating arteries, and hydrocephalus. Paradoxical manifestation is very common in non-HIV TBM, seen in 56% of the University Malaya Medical Centre patients. Paradoxical manifestation is worsening of pre-existing tuberculous lesion or appearance of new lesions in patients whose condition initially improved with antituberculous treatment. The phenomenon of paradoxical manifestation is said to be due to exaggerated immune response to the mycobacterial antigen.

5.3. Clinical features

Patients with TBM can present with seizures. At the mentioned hospital, 20% of TBM patients had seizures during presentation.

Seizures can also occur during the course of the treatment, due to the encephalitis, tuberculoma, vasculitic, hydrocephalus, hyponatraemia and isoniazid. At the same hospital TBM patients with paradoxical manifestation, 22% had seizures. Seizures in TBM can also lead to status epilepticus, with its consequential morbidity [40].

6. Other neglected emerging infections

Japanese encephalitis virus is a flavivirus transmitted by mosquitoes from bird and pigs to human. It is mainly found in East, South and South East Asia. It causes 20,000–50,000 infections and 15,000 deaths annually. It is thus the most important viral encephalitis globally. The virus causes diffuse encephalitis, particularly affecting the midbrain, thalamus, and basal ganglia. Seizures occur in approximately 40–60% of patients; the rate is as high as 80% in children. Other than the focal and generalized seizures, up to a quarter may have status epilepticus, which may be subtle. Seizures herald a poor prognosis, and are associated with a high mortality [41].

West Nile virus is a flavivirus endemic in Africa and the Middle East. In 1999, the infection spread to New York, and subsequently spread across the United States to reach the Pacific coast. About 20% of patients infected with the virus develop a mild febrile illness and 1 in 150 develops central nervous system infection. Seizures occur in 5–30% of patients with encephalitis, and often present during the later part of the illness [42].

Dengue virus is another flavivirus. It causes one of the most important viral infections globally, affecting over 50 million yearly, with half a million hospital admission. The virus is pandemic in South and South East Asia and South America. Febrile illness with rash and thrombocytopenia is the hall mark of the illness. Vascular leakage with shock and hemorrhage are manifestations of dengue shock syndrome and dengue hemorrhagic fever. Neurological involvement is seen in 5% of patients with dengue fever. The mechanism may be complications of hemorrhage, vascular leakage or hepatic failure, immune mediated disorder such as Guillain–Barré syndrome, or possible direct viral involvement. Approximately 10–15% of those with neurological involvement have seizures. The overall mortality of dengue infection is low. However, among the patients with central nervous system involvement, the mortality is 30%, with another 20–30% having long-term deficits [43].

Nipah virus is a paramyxovirus endemic among the fruit bats in South and South-East Asia and in African coastal regions. In 1998, it caused a fatal outbreak of encephalitis in Malaysia and Singapore. Subsequent outbreaks occurred in Bangladesh, India, and the Philippines. The infections are thought to spread from bats through contaminated food such as raw date palm juice, contact with infected animals such as pigs, dogs or horses, and human-to-human spread. Other than a fatal encephalitis and chest infection, Nipah virus may also cause relapsed encephalitis, which may occur years after the initial infection. Seizure is seen in a quarter of patients during acute encephalitis, and half of the patients during relapsed encephalitis. Segmental myoclonus is also commonly seen in acute encephalitis, especially those with more severe disease [44,45].

Enterovirus are small RNA viruses that belong to the family of *Picornavidae*. There are many serotypes and human is the only host. They are mainly transmitted by fecal–oral route or respiratory droplets. Some serotypes are more likely to cause central nervous system infection, among these, enterovirus 71 which has caused large outbreaks all over the world. Since the late nineteen nineties, frequent outbreaks have occurred in many Asian countries. Clinically, enterovirus 71 mainly affect children, those below 5 years are particularly severely affected. Enterovirus causes a variety of symptoms, including hand-foot-and-mouth disease and myocarditis. In the nervous system, it can cause aseptic meningitis, encephalitis, and in particular, rhombencephalitis, which is associated with fatal pulmonary oedema. Among children with rhombencephalitis, majority has myoclonic jerks. Seizures and opsoclonus have also been documented [46].

As for the non-viral infection, other than tuberculosis, other infections that may result in seizures as important manifestation include leptospirosis from *Leptospira*, and typhus from *Rickettsia*. Seizure has been reported to be seen in a third of patients with leptospirosis and status epilepticus in 15% of scrub typhus [47,48].

7. Other neglected emerging diseases

Other than infectious disease, there are other diseases that are emerging in the tropics. There are explosion of new autoimmune encephalitis being reported in the last decade. Among the newly discovered disease is anti-NMDAR encephalitis, which typically affect young females. There are some evidence to indicate that anti-NMDAR encephalitis may be more common among some non-Caucasian populations.

There are some evidence to indicate that anti-NMDAR encephalites may be more common among some non-Caucasian populations, as reported in Malaysian and Thai studies describing close to half and 6% respectively of all analyzed encephalites [48]. Epileptic seizures and status epilepticus are common manifestations of anti-NMDAR encephalitis which require immune therapy as well as anti-epileptic drugs [47,48].

Systemic lupus erythematosus is also relatively more common among the East Asians. In the Thai encephalitis study mentioned above, cerebral lupus accounted for 4% of the encephalitis. Seizure is an important manifestation of acute cerebral lupus [48].

Traumatic brain injury is another emerging cause of epileptic seizures in the tropics. Many tropical countries are enjoying robust economic growth, with rapid increase in the motor vehicles. Serious brain injury per vehicle is much more common in the developing countries as compared to the developed countries. According to WHO, in 2010, the road fatality is 5–10 per 100,000 motor vehicles per year in the developed countries, whereas it is 15 times higher (30–250 per 100,000 motor vehicles per year) in many developing countries. As example of the increasing trend of traumatic brain injury, the Ministry of Health in Vietnam reported 6000 road traffic deaths in 1998. It rose to 14,700 deaths in 2008, and 22,400 in 2013. Early seizures (within one week after injury) occur in 4–7% of post-traumatic brain injury, and late-seizures (after 1 week) in 9–42% [49,50].

Conflict of interest statement

The authors declare no conflicts of interest.

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