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Review

Parasites and epilepsy: Understanding the determinants of epileptogenesis

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ABSTRACT

There is a large body of evidence suggesting that parasites could be a major preventable risk factor for epilepsy in low- and middle-income countries. We review potentially important substrates for epileptogenesis in parasitic diseases. *Taenia solium* is the most widely known parasite associated with epilepsy, and the risk seems determined mainly by the extent of cortical involvement and the evolution of the primary cortical lesion to gliosis or to a calcified granuloma. For most parasites, however, epileptogenesis is more complex, and other favorable host genetic factors and parasite-specific characteristics may be critical. In situations where cortical involvement by the parasite is either absent or minimal, parasite-induced epileptogenesis through an autoimmune process seems plausible. Further research to identify important markers of epileptogenesis in parasitic diseases will have huge implications for the development of trials to halt or delay onset of epilepsy.

1. Introduction

The burden of epilepsy seems to be higher in low- and middle-income countries where parasitic diseases are also endemic [1]. There is persuasive evidence associating epilepsy with a wide range of parasites [2]. For example, neurocysticercosis is responsible for at least one-third of epilepsy in many parts of Asia, Latin America, and sub-Saharan Africa (SSA) [3–9]. Parasites that have been linked with epilepsy can broadly be classified as microparasites (*Plasmodium spp*, *Toxoplasma spp*, and *Trypanosoma spp*) and macroparasites, which are mostly helminths (*Toxocara spp*, *Onchocerca volvulus*, *Paragonimus spp*, *Spirometra mansoni*, *Schistosoma spp*). This distinction is important as the potential mechanistic consideration for epileptogenesis may vary between them; while microparasites most likely cause epilepsy through their capacity given their small size to invade the brain directly, macroparasites may depend on the neurotropic properties of their eggs or larvae and/or other indirect mechanisms to predispose to epilepsy. Much is known about brain involvement in malaria and cysticercosis because of the large populations they impact as well as the unmistakable neurological complications associated with them. Other neurotropic parasites have received less attention, either as they are limited to specific geographic regions (paragonimiasis, schistosomiasis, and trypanosomiasis, sparganosis) or as the evidence supporting brain involvement is lacking (onchocerciasis). Acute brain involvement, however, represents only the tip of the iceberg in parasitic diseases, with respect to the epilepsy risk in the affected individual. A large proportion of those exposed to these parasites remain asymptomatic yet may still have a significantly increased risk of epilepsy [2]. For example, while latent infection with *Toxoplasma spp* and *Toxocara spp* is generally considered to be asymptomatic, ubiquitous exposure to these parasites means that even a modest increase in the risk of epilepsy could significantly contribute to the high burden of epilepsy worldwide. We briefly review parasites which commonly predispose to epileptic seizures and discuss factors likely relevant in the epileptogenic process. Understanding the mechanisms underpinning epileptogenesis in parasitic diseases may be critical in developing interventions for the primary and secondary prevention of epilepsy associated with parasites.

Abbreviations: BBB, blood–brain barrier; HS, hippocampal sclerosis; IPI, initial precipitating injury; MMP-9, matrix metalloproteinase-9; MTLE, mesiotemporal lobe epilepsy; PCR, polymerase chain reaction; RBC, red blood cell; SSA, sub-Saharan Africa; Th, T helper.

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2. Parasitic diseases commonly associated with seizures and epilepsy

2.1. Malaria

Over one-third of the world population is exposed to malaria, mainly in Africa [10] where it is one of the main triggers of seizures, especially among children. Seizures are a common occurrence in children with malaria, and some of these may be simple febrile seizures. The majority of the seizures are, however, prolonged, have focal characteristics, and occur when temperature is less than 38 °C, implying that other mechanisms besides fever, probably directly related to the parasite, are involved [11,12]. Seizures also occur after recovery from the acute malaria episode, especially after cerebral malaria. In one study, about 10% of children with cerebral malaria followed up over a substantial period developed epilepsy [13]. *Plasmodium falciparum* is responsible for most cases of malaria in SSA *and* is transmitted through bites of the female anopheles mosquito leading to the invasion of red blood cells (RBCs) [10]. Cerebral malaria is the most serious, often fatal presentation of falciparum malaria, particularly in children in SSA [14]. Parasitic invasion of the cerebral vasculature is the main pathophysiological mechanism and is thought to be responsible for the acute clinical presentation and neurological sequelae. Typically, the plasma membranes of parasitized RBCs form knobs containing proteins that facilitate their adhesion to the endothelial surface of cerebral vasculature [15]. Through this process, parasitized RBCs progressively become sequestered within the cerebral microcirculation and form rosettes with uninfected RBCs, thereby compromising blood flow, leading to ischemia and the release of inflammatory cytokines [16,17].

2.2. Taeniasis/Cysticercosis

Neurocysticercosis is the most severe manifestation of infestation by *Taenia solium* and is believed to be responsible for at least one-third of epilepsy cases in endemic regions in Africa, Latin America, and Asia [6,18]. A recent systematic review estimated that almost two-thirds of epilepsy cases in areas where cysticercosis is endemic are attributable to it; this is even higher for late-onset epilepsy [19]. In the parasite lifecycle, humans become infected by consuming cysts contained in raw or poorly cooked pork from infected pigs (intermediate hosts); the cysts develop into the adult tapeworm in the intestines (Taeniasis), and eggs passed out in feces contaminate the environment where they are ingested by free-ranging pigs. Neurocysticercosis, however, occurs when humans become aberrant intermediate hosts by ingesting eggs that develop into larvae called onchospheres, which from the intestines, enter the circulatory system and reach the brain or other tissues where they form cysts. How the parasite traverses the blood–brain barrier (BBB) and into the brain parenchyma is poorly understood. Some have suggested that neurotropism may be determined by genetic factors in certain parasite species [20]. Parasites found in the cerebral parenchyma usually evolve through four main stages: vesicular, colloidal, granular–nodular, and granulomatous/calcified stages. The vesicular stage is characterized by a viable cyst containing parasite antigens with immunological properties that enable it to avoid attack by the host immune system [21]. In the colloidal (active) stage, the cyst enters a degenerative phase, releasing antigens that trigger an intense inflammatory response [22]. The parasite then progressively degenerates through the granular–nodular stage to either complete involution or a calcified lesion [23]. Seizures can occur at any stage of neurocysticercosis, although the provoking factors are different (see Section 3.1). Neurocysticercosis cysts can also be found in extraparenchymal structures (racemose variant), and the symptoms depend on the location and number of lesions [24].

2.3. Onchocerciasis

Onchocerciasis is caused by microfilariae of *Onchocerca volvulus*, and it is the leading cause of blindness in parts of Africa [25]. There is, however, accruing evidence from case–control studies associating it with epilepsy [26]. Epilepsy prevalence has been shown to increase with proximity to rivers, which are breeding grounds for the vector, the simulium fly [27,28]. There is also a positive correlation between hyperendemicity of onchocerciasis and high prevalence of epilepsy [29]. Recent evidence from a cohort study in Cameroon suggests a temporal relationship and etiological gradient between onchocerciasis and epilepsy [30]. Further evidence of a possible causal relationship between onchocerciasis and epilepsy comes from studies implicating onchocerciasis in a childhood epileptic encephalopathy, nodding syndrome. This is characterized by head nodding usually starting around the age of six years followed by cognitive decline and behavioral problems [31]. Clinical studies of nodding syndrome show that other seizure types are a common feature, sometimes, with familial clustering of such cases [31,32]; this reinforces the argument that nodding syndrome is part of a spectrum of seizure disorders in people with epilepsy associated with onchocerciasis. While there seems to be consistent evidence in favor of a causal relationship between onchocerciasis and epilepsy, further studies are needed to confirm this hypothesis, especially given that plausible biological mechanisms of causality remain hypothetical.

Humans are the only definitive host of *Onchocerca volvulus*, and its larva are introduced by the vector (simulium fly). The larva develops into an adult worm, and the female locks itself up in a subcutaneous fibrous capsule and releases microfilariae that mainly migrate to the skin and eye [33]. Microfilariae in the eye provoke neutrophil and eosinophil infiltration and the release of cytokines into the corneal stroma resulting in corneal opacification and blindness [34]. *Wolbachia* are rickettsiae transmitted simultaneously with *Onchocerca volvulus* by the simulium fly which, by promoting larval development and worm fertility, are important in the pathogenesis of onchocerciasis and its complications [35]. There is no strong evidence yet of the presence of microfilariae in the brain, although this does not exclude direct or indirect effects of microfilariae; there seems to be a correlation between positive skin polymerase chain reaction (PCR) to *Onchocerca volvulus* and Magnetic Resonance Imaging (MRI) abnormalities in nodding syndrome [36].

2.4. Toxocariasis

Toxocariasis is a zoonosis caused by larvae of *Toxocara spp*, a nematode that inhabits the gut of dogs (*Toxocara canis*) and cats (*Toxocara catis*). In humans, ingested embryonated eggs persist in the juvenile larval stages, penetrate through the gut wall, and migrate to several body organs. Two broad clinical syndromes of toxocariasis can be distinguished: visceral larva migrans (a systemic inflammatory response to multiple organ involvement) and ocular larva migrans (eye and optic nerve involvement). Cerebral involvement causes a variety of acute neurological syndromes including seizures [37]. The term "covert toxocariasis" describes chronic infection that is either asymptomatic or associated with only mild and nonspecific symptoms. This condition is, however, being increasingly associated with an increased risk of epilepsy in low- and high-income countries [38].

2.5. Toxoplasmosis

Chronic toxoplasmosis is ubiquitous and has been traditionally considered asymptomatic in immunocompetent people but is increasingly linked with epilepsy [39]. It is caused by *Toxoplasma gondii*, an obligate intracellular protozoan [40]. Cats are the only known definitive hosts, and they shed large quantities of oocysts of the parasite in their feces [41]. Humans are intermediates hosts, and after cysts are ingested from contaminated food sources, the parasite traverses the intestinal lumen and migrates to the brain with the help of macrophages. Parasites in the neurons undergo proliferation while those in microglial cells upregulate genes encoding proinflammatory and antiinflammatory cytokines resulting in chronic infection, ensuring survival of the host while maintaining the parasite in a dormant state [42,43].

2.6. Schistosomiasis

Schistosomiasis is caused by the trematode, *Schistosoma spp*, which affects over 200 million people, mostly in Africa [44]. It may be an important risk factor for epilepsy in affected communities. Human disease occurs through contact with fresh water containing free-swimming larvae called cercariae, which penetrate the skin, enter the venous circulation, and migrate through the portal circulation to the mesenteric veins or the vesical plexus to produce eggs [44]. The eggs pass into the lumen of the intestines (*S. japonicum* and *S. mansoni*) and the bladder (*S. haematobium*) and are shed in feces or urine [44]. The eggs reach the brain either by embolization through arteriovenous/portosystemic shunts or by migration of the parasite through the vertebral venous plexus into the brain parenchyma or meninges to lay eggs *in situ* in clusters [45]. The inflammatory reaction to the parasite ranges from mild inflammation around scattered ova to severe periovular inflammation, forming giant granulomas [46]. In endemic areas, cerebral invasion can affect over 1/4 of the population, most of whom are asymptomatic [47]. Case reports suggest that seizures can occur several years after exposure to *Schistosoma spp* [48,49].

2.7. Paragonimiasis

Seizures are the most common presentation of cerebral paragonimiasis [50]. This food-borne disease is caused by *Paragonimus spp*, a trematode endemic in countries with freshwater bodies where the intermediate hosts live [51]. *Paragonimus westermani* is the main species responsible for human paragonimiasis. Humans are the definitive host and become infected after consumption of the larvae from raw or poorly cooked crustaceans. Adults live in pairs in the lungs and form cysts that rupture into airways, releasing eggs that are either expelled in sputum or swallowed and passed in feces [52]. The parasites reach the brain either by direct migration from the lungs through the jugular foramen or through embolization of its eggs [53,54]. Cerebral paragonimiasis is the most common form of extrapulmonary paragonimiasis and accounts for over 50% of such cases [54]. It is also a great mimic of cerebrovascular disorders [55–57].

2.8. Sparganosis

Sparganosis was associated with epilepsy in one Korean case–control study, reporting an odds ratio of 1.3 [58]. It is caused by sparganum, the plerocercoid larva of the cestode, *Spirometra mansoni*. This parasite is only seen in Asia, mostly limited to China, Japan, Korea, and Taiwan [59]. Cats and dogs are the definitive host and harbor adult worms that shed eggs that are passed out in feces and evolve through several larval stages within intermediate hosts in fresh water. Human disease results either from drinking water contaminated with copepods or from eating poorly cooked intermediate hosts that contain sparganum. Cerebral involvement is usually chronic and presents as recurrent headaches or epileptic seizures, although it may mimic a brain tumor [59].

2.9. Human African trypanosomiasis (HAT)

Seizures are one of the main symptoms in the chronic stage of HAT. This is limited to rural communities in SSA where its vector (tsetse fly) is found, although sustained control efforts by the World Health Organization (WHO) have led to near-elimination in most countries [60]. It is caused by the protozoa Trypanosoma, and *Trypanosoma brucei gambiense* is responsible for almost all cases. It is transmitted to humans by bites from infected tsetse flies that acquire the infection by biting infected humans or animals. Cerebral involvement occurs in chronic infestation when the parasites cross the BBB to the Central Nervous System (CNS).

3. Mechanistic considerations for epileptogenesis in parasitic diseases

3.1. Distinguishing between acute symptomatic seizures and remote symptomatic seizures

It is important to distinguish between acute and remote symptomatic seizures when discussing seizures related to parasitic diseases [61]. Acute symptomatic seizures are the result of temporary disturbances in neuronal function, mainly due to inflammation in the cerebral cortex directed against the parasite; they often subside when the inflammation stops [62]. Conversely, remote symptomatic seizures are usually recurrent and probably result from long-term structural and functional changes in the brain parenchymal networks causing hyperexcitation and synchronization of neurons (Table 1). Neurophysiological and imaging studies, when available, are helpful in diagnosing acute symptomatic seizures; focal electroencephalogram (EEG) abnormalities usually correlate with lesion location and "activity" on MRI [63].

Epileptogenesis is the development and extension of tissues capable of generating spontaneous epileptic seizures, including the development of epilepsy and progression after the condition is established [64]. Brain invasion by the parasite contributes to this process by causing several structural changes in the cerebral cortex: cerebrovascular lesions; calcification; gliosis; and hippocampal sclerosis (HS). These cerebral lesions alone may not suffice for the development of epilepsy in an individual. For example, they do not explain epileptogenesis in cases where brain involvement is either limited or absent. Other host and parasite-specific factors may thus be necessary for the development and progression of enhanced excitation and synchronization of cortical networks. Below, we present factors that may be important triggers or catalysts of epileptogenesis (Figs. 1–3).

3.2. Epileptogenic cortical insults

3.2.1. Cerebrovascular lesions

Vascular insults involving the cerebral cortex can lead to epilepsy. Cerebrovascular disorders engender unprovoked seizures due to the deposition of products of blood decomposition (in hemorrhagic stroke), neuronal cell loss, and reorganization of neuronal circuitry favoring synchronization in the cerebral cortex [65]. Cerebral paragonimiasis and schistosomiasis affect large vessels and may mimic cerebrovascular disorders in causing hemorrhage and vascular obstruction [66,67]. Stroke resulting from occlusion of the large arteries at the base of the brain, as well as of the deeper penetrating arteries, is a recognized manifestation of neurocysticercosis, particularly the meningeal-racemose variety [24]. In cerebral malaria, central parasitemia and raised excitotoxic amino acids cause hypoxic–ischemic events that may be responsible for structural brain changes [68–70]. Magnetic Resonance Imaging of survivors of cerebral malaria 6–24 months after onset of neurological sequelae show several types of lesions of probable epileptogenic potential: periventricular T2 signal changes, atrophy, and focal cortical defects [71]. Sonographic abnormalities associated with lateralization deficits are common in children with cerebral malaria who develop neurological sequelae, and this suggests some structural or perfusion perturbations as the cause of the deficit [72]. Occasionally, the vasculopathy and perivascular inflammation and edema lead to demyelination and the formation of a granuloma (Durk's Granuloma) [73], which could all lead to recurrent seizures.

3.2.2. Calcified lesions

The evolution of a parasitic brain lesion to a calcific granuloma is most commonly encountered in cerebral paragonimiasis and neurocysticercosis but can occur in any brain invasion where granulomatous inflammatory lesions are formed. In neurocysticercosis, the evolution of the granuloma to a calcified lesion seems to be a strong predictor of seizure recurrence [74]. Perilesional edema around the calcified lesions seems to be critical in determining their epileptogenic

Table 1
Causes of early reactive and late seizures in parasitic diseases.

Parasite	Disease	Cause of acute symptomatic seizures	Probable causes of remote symptomatic seizures
Plasmodium falciparum (microparasite)	Malaria	Hypoxic–ischemic effects of parasitized RBCs on cerebral microvasculature; fever; anemia; electrolyte disturbance; hypoglycemia	1. Parenchymal brain damage due to effects of coma and central parasitemia 2. Kindling effect of malaria-associated seizures, febrile seizures, and status epilepticus 3. Demyelination, gliosis, and granuloma
Taenia solium (macroparasite)	Neurocysticercosis	Larval antigens cause release of inflammatory cytokines, breakdown of the BBB, and neoangiogenesis	1. Evolution of cyst to calcified granuloma with accompanying perilesional edema 2. Hippocampal sclerosis due to gliosis 3. Kindling effect of acute symptomatic seizures and chronic low-level inflammation in the calcified granuloma
Onchocerca volvulus (macroparasite)	Onchocerciasis	No known acute neurological features	1. Autoimmune phenomena 2. Brain invasion by microfilariae or *Wolbachia*
Toxocara spp (macroparasite)	Toxocariasis	Very little inflammation in the acute phase so seizures are rare	1. Chronic infestation increases neurotropism of the parasite and risk of brain damage 2. Astrogliosis 3. Increased expression of proinflammatory cytokines 4. Disturbances in neurotransmitter profile, favoring excitation
Toxoplasma gondii (microparasite)	Toxoplasmosis	*Immuno-compromised hosts*: multiple focal parenchymatous inflammatory lesions and encephalopathy *Immunocompetent hosts*: little or no inflammation	1. Neuronal damage by the parasite 2. Production of excitotoxic substances and reactive oxygen species 3. Gene upregulation, manipulation of behavior, and reduced psychomotor performance, exposing to other acquired risk factors of epilepsy such as head injury
Schistosoma spp (macroparasite)	Schistosomiasis	Periovular inflammation and formation of granuloma, Cerebral hemorrhage	1. Gliosis from granulomata in the acute infection or from asymptomatic ova deposition 2. Cortical irritation caused by blood products from cerebral hemorrhage
Paragonimus westermani (macroparasite)	Paragonimiasis	Inflammation, arteritis, hemorrhage, and mass effect	1. Calcified lesion 2. Gliosis
Spirometra mansoni (macroparasite)	Sparganosis	Granulomatous reaction	Gliosis
Trypanosoma brucei gambiense (microparasite)	Human African trypanosomiasis		Neuronal loss

potential [75–77]. The edema results from intermittent exacerbations in inflammation, possibly driven by periodic release of antigenic remnants of the parasite in the calcified lesion [78]. On pathological examination, perilesional edema typically consists of mononuclear infiltrates in the capsule around the calcified cyst extending to the adjacent brain, which also shows signs of marked gliosis, astrocytosis, and perivascular infiltrates [79]. Even in situations where seizures occur in the absence of obvious perilesional edema, it has been suggested that undetectable low levels of inflammation may still be sufficient to generate seizures or facilitate kindling of the hippocampus [80]. Apart from perilesional edema, calcified cysts could also provoke seizures through the toxic effect of calcium itself on the surrounding cortex [81].

3.2.3. Gliosis

Gliosis may occur after recovery from the acute brain inflammation associated with parasitic infection. Gliosis is most significant in parasitic diseases such as neurocysticercosis, paragonimiasis, schistosomiasis, and sparganosis where brain involvement is associated with significant inflammation around the affected cortical tissue. In neurocysticercosis, gliosis around the cyst is known to predict seizure recurrence and refractory seizures [82,83]. This is supported by histological evidence of gliosis surrounding lesions after resection in people with intractable epilepsy [79]. One prospective study reported that people with neurocysticercosis with perilesional gliosis had more contralateral abnormal motor phenomena, corresponding with EEG abnormalities than people with neurocysticercosis without perilesional gliosis; these subtle "interictal" symptoms could be epileptic phenomena associated with the perilesional gliosis [84].

3.2.4. HS

Because of their increased excitability, mesiotemporal structures have a higher tendency than other parts of the brain to be involved in epileptic seizures, even when the focal lesion is located elsewhere in the cerebral cortex [65]. Consequently, by their invasion of mesiotemporal structures or other parts of the cortex with networks linked to the hippocampus, some parasites increase the risk of HS. Cerebral malaria has been shown to lead to hippocampal damage in children [85]. Experiments in mice show that cerebral malaria interferes with hippocampal neurogenesis and increases hippocampal cell death [86]. Some studies suggest a link between neurocysticercosis and mesiotemporal lobe epilepsy with HS (MTLE-HS) [87–89]. There also seems to be a correlation between the side of the HS and that of the calcified cysts [88,90–92]. Neurocysticercosis may cause MTLE by provoking the initial precipitating injury (IPI) that leads to HS, as MTLE and neurocysticercosis occur more commonly together among older people and those lacking a classical IPI [88,90]. The IPI could result from the perilesional edema around a calcified lesion located in the temporal lobe, mediated by increased expression of matrix metalloproteinase-9 (MMP-9) [93]. In animal experiments, there is preferential expression of MMP-9 in the dentate gyrus of the hippocampus following stimulation with a glutamate receptor (kainate), suggesting that it may be involved in activity-dependent remodeling of dendritic architecture with possible effects on synaptic physiology [94].

3.2.5. Kindling effects of febrile seizures and acute symptomatic seizures

In acute cerebral insult, the occurrence of acute symptomatic seizures increases the risk of remote symptomatic seizures [65]. Malaria-associated seizures are mostly of a complex phenotype and, together with febrile seizures, are associated with an increased risk of developing epilepsy after recovery [13,95]. In neurocysticercosis, the inflammatory cascade around the degenerative cyst, especially in the colloidal stage, is the main trigger of acute symptomatic seizures [96]. These seizures are often complex, occurring in clusters and with status epilepticus being common [97]; they probably predispose to epilepsy by engendering

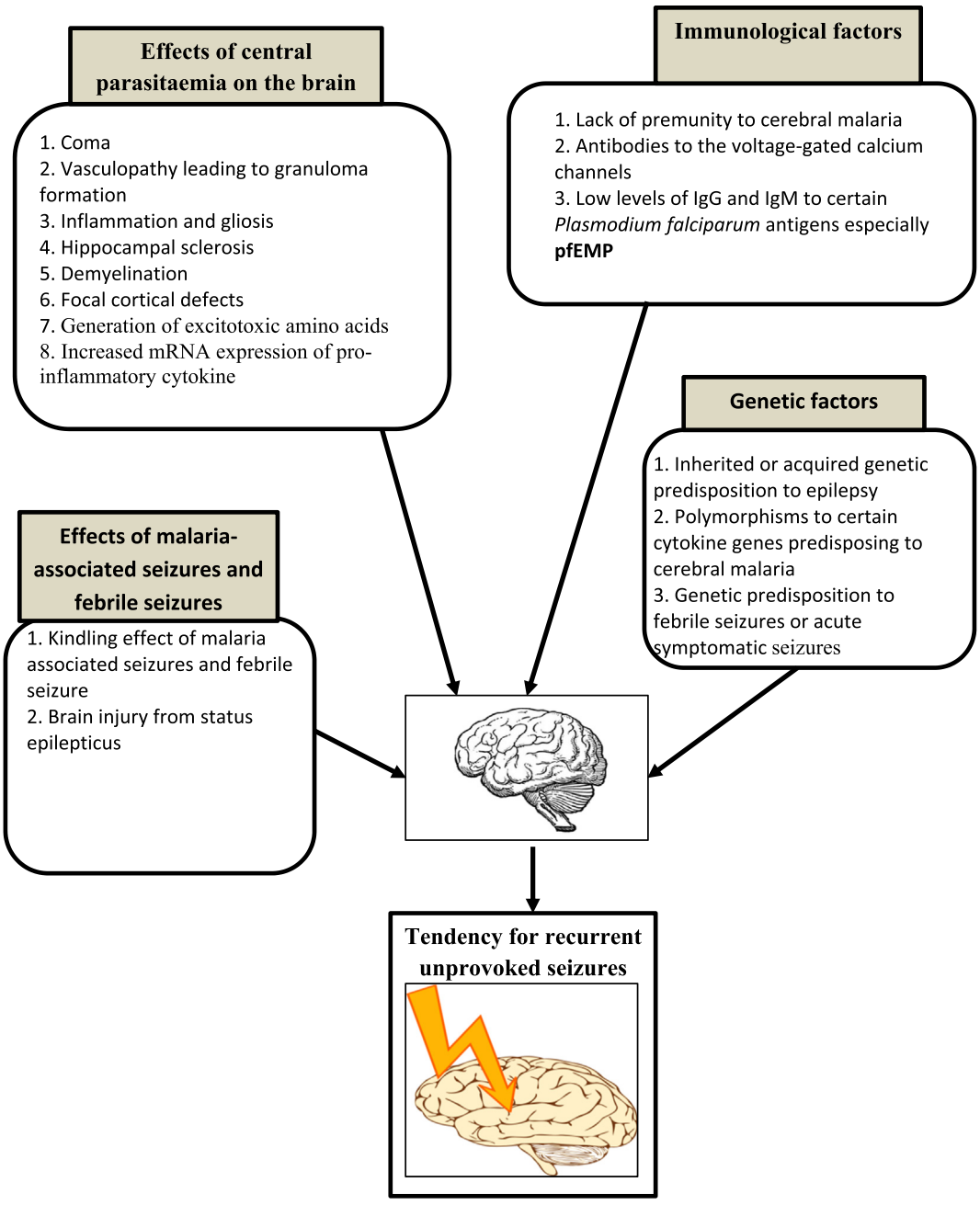

Fig. 1. Possible epileptogenic substrates of malaria.

the development of secondary epileptogenic lesions [98,99]. Secondary epileptogenic lesion formation is thought to result from downhill morphological changes, mostly along the corpus callosum, from the propagation of continuous epileptiform discharges [65].

3.2.6. Alteration of neuronal function

Toxoplasma gondii affects neuronal function through a variety of ways (Table 1): direct neuronal damage; disturbance in serotonin metabolism leading to tryptophan depletion; and increased production of substances such as quinolinic acid [100]. Quinolinic acid is an N-methyl-D-aspartate (NMDA) receptor agonist that can provoke seizures and, together with similar substances, can also cause neuronal death by facilitating the production of reactive oxygen species [100]. These substances, through their excitotoxic effects on neurons, may alter the balance between excitation and inhibition in the cortex, predisposing to epilepsy.

3.3. Immunological considerations

In situations where cortical involvement by the parasite is either absent or minimal, autoimmune phenomena could be triggers or catalysts of epileptogenesis. Similarities have been shown between E1 antigens of *Onchocerca volvulus* and some neuronal antigens [101], raising the possibility of an autoimmune mechanism (similar to that which occurs in the skin manifestation of the disease) as the cause of epilepsy in onchocerciasis. The autoimmune hypothesis has been reinforced by evidence from a recent study of nodding syndrome showing that antibodies to leiomodin-1, a protein that is cross-reactive with *Onchocerca volvulus* antigens, are more common in the sera and the cerebrospinal fluid (CSF) of people with nodding syndrome than in healthy subjects. The researchers also demonstrated that anti-leiomodin-1 antibodies are neurotoxic and that

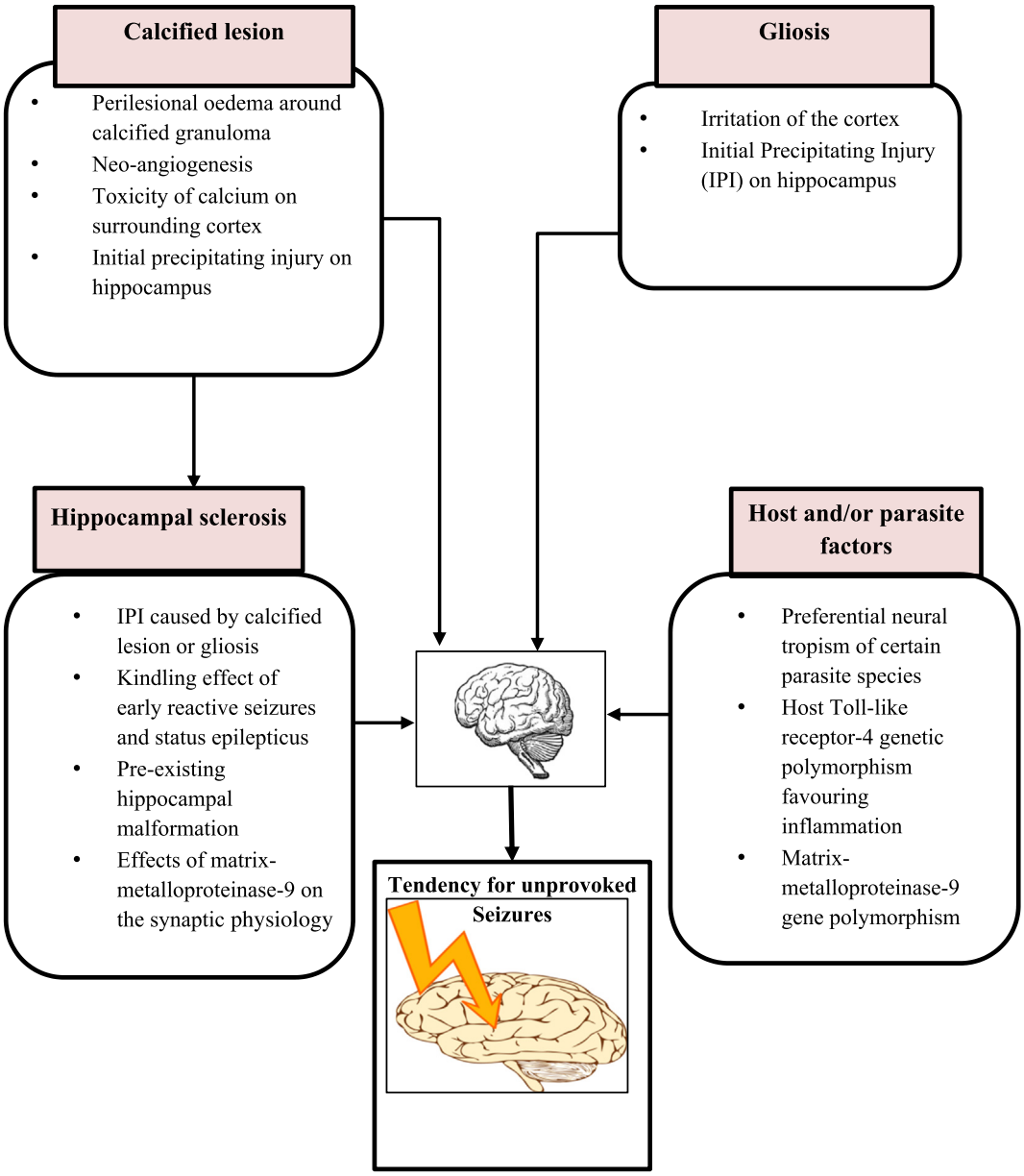

Fig. 2. Possible epileptogenic substrates in neurocysticercosis.

leimodin-1 is preferentially expressed in parts of the mouse brain similar to those of people with nodding syndrome [102].

Immunity to severe forms of parasitic infestations, or lack thereof, could also determine the risk of epilepsy. Immunological response to malaria is complex, and although a substantial reduction of the transmission of plasmodium through vector control probably reduces the incidence of malaria and hence the risk of epilepsy, this effect is diluted by the increased risk of cerebral malaria in immunologically naïve children at an older age [103]. Some have shown that low levels of IgM and IgG against certain *Plasmodium falciparum* antigens may predispose to severe malaria and that an imbalanced proinflammatory cytokine response may exacerbate the severity of infection and perhaps, the risk of epilepsy [104]. Acquired immunity due to constant exposure to onchospheres of *Taenia solium* seems to be important in mitigating the severity of neurocysticercosis and the risk of epilepsy [105].

3.4. Genetic factors

In general, genetic predisposition might occur at four different levels: genetic predisposition to parasitic disease; genetic factors that determine the nature of the inflammatory response mounted in the brain against the parasite; genetic predisposition to acute seizures during infection; genetic susceptibility to unprovoked seizures. A preexisting genetic predisposition to epilepsy, which was previously subclinical, may become clinically evident because of the development of a potentially epileptogenic parasitic brain lesion. Epilepsy susceptibility genes may be present because of sporadic genetic mutations, or inherited from parents, who themselves may not be clinically affected by epilepsy. In cerebral malaria, a family history of epilepsy is significantly associated with an increased risk of epilepsy and an adverse neurological outcome [106,107]. One African study showed that children admitted with falciparum malaria may have a genetic predisposition to acute seizures [12]; it is not clear how this impacts on the risk of epilepsy. In a large genetic study among Gambian children, it was concluded that polymorphisms for certain cytokine genes such as homozygotes of the Tumor-necrosis factor 2 (TNF2) allele, implicated in the pathogenesis of cerebral malaria, may be associated with a sevenfold increase in the risk of death and neurological sequelae after cerebral malaria [108]. In neurocysticercosis, genetic factors in certain hosts play an important role in determining the severity of the inflammatory

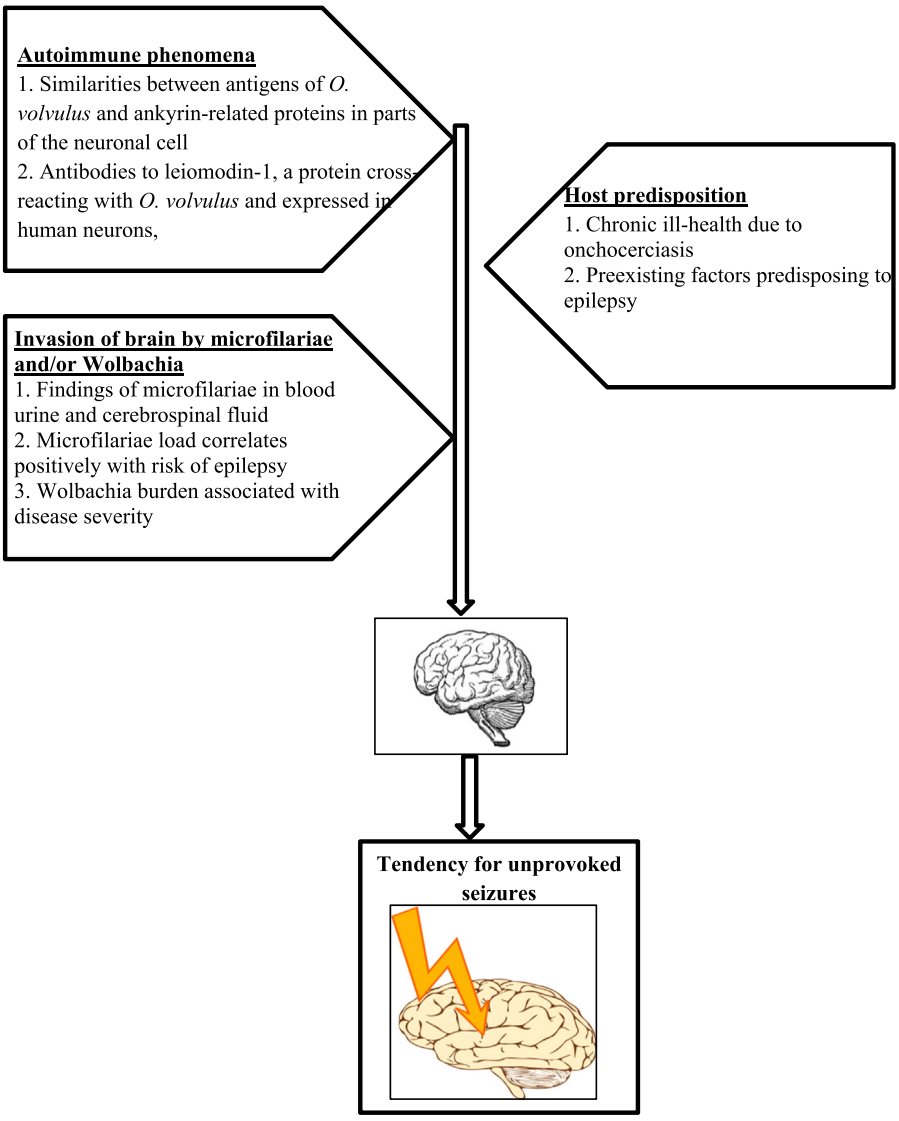

Fig. 3. Possible epileptogenic pathways of onchocerciasis.

response. There is evidence showing that Toll-like receptor 4 (TLR4) genetic polymorphism is a risk factor for the development of epilepsy in people with neurocysticercosis, by contributing to alteration of the Th1/Th2 axis, favoring inflammation [109]. In one study, significantly higher MMP-9 gene polymorphism with differential upregulation of MMP-9 was observed in people with symptomatic NCC compared with those with no symptoms [93]. From pathological studies of cerebral malaria in humans and animals, it can be speculated that an imbalance between factors promoting brain injury and neuroprotective factors such as nuclear factor kappa-B and neuroglobin contributes to the epilepsy risk [110,111].

3.5. Favorable parasite-specific factors

Some parasites may accelerate the epileptogenic process by predisposing affected individuals to other risk factors of epilepsy. Studies show that toxoplasmosis can lead to manipulation of behavior and reduced psychomotor performance through its effect on dopamine and testosterone [112]. People with chronic toxoplasmosis are at increased risk of road traffic accidents [113–115] which could, in turn, increase the risk of posttraumatic epilepsy. Behavioral manipulation by toxoplasma could also predispose to epilepsy by promoting exposure to other parasites that cause epilepsy. People with toxoplasmosis have twice the odds of being coinfected with *Toxocara spp*, another risk factor for epilepsy [116]. There is also some suggestion that multiple parasite exposure, especially if including toxoplasmosis or onchocerciasis, could further increase the epilepsy risk beyond the additive risk of the individual parasites [117].

Certain parasite species, by their predilection for neural tropism, confer a higher epileptogenic risk than those with less neural tropism. In neurocysticercosis, it has been postulated that differences in neural tropism, conferred by the genetic differences between species of *Taenia solium*, are partially responsible for variations in the risk of neurocysticercosis and epilepsy observed between similar pig-rearing communities [20]. This genetic variation appears to be promoted by concomitant immunity exhibited by pigs to cysticerci from different geographical regions [118].

Through their endosymbiotic relationship with certain parasites, some pathogens could either provoke an epileptogenic lesion in the brain or facilitate the progression of an epileptogenic lesion initiated by the parasite itself. Onchocerciasis could cause epilepsy indirectly through a hypothetical indirect mechanism involving *Wolbachia*, which is cotransmitted with Onchocerca microfilariae and is known to play a role in the pathogenesis of river blindness. Chronic filariasis has a modulatory effect on the immune system [119]. It is possible that the death of microfilariae releases *Wolbachia* antigens, triggering an

inflammatory response that results in the breakdown of the BBB, enabling access of either microfilaria or *Wolbachia*, or both, into the brain. Epileptic seizures could then result from a sustained inflammatory response leading to neuronal loss and gliosis as a result of repeated exposure to *Wolbachia*. If this was the case, one would expect *Wolbachia* or inflammatory markers in the CSF to reflect the ongoing inflammatory process. These have not been shown so far [120]. While there is some suggestion that good therapeutic coverage with ivermectin may have resulted in a reduction in the incidence of epilepsy in some endemic areas [121], it is important that this is further investigated using robust prospective studies. It would be interesting to investigate whether ivermectin has any effect on *Wolbachia* and whether antibacterial treatment targeting *Wolbachia* would have any effect on epilepsy incidence, providing indirect evidence of a *Wolbachia* role in the development of epilepsy.

4. Conclusion

Taenia solium is the most widely known parasite associated with epilepsy, and epilepsy risk seems determined mainly by the extent of cortical involvement and the evolution of the primary cortical lesion to gliosis or to a calcified granuloma. For most parasites, however, epileptogenesis is more complex, and other favorable host genetic factors and parasite-specific characteristics may be critical. In situations where direct cortical involvement by the parasite is either absent or minimal, parasite-induced epileptogenesis through an autoimmune process seems plausible. Further research to identify important markers of epileptogenesis in parasitic diseases will have huge implications for the development of trials to halt or delay onset of epilepsy in endemic areas.

Conflict of interest

The authors have nor conflict of interest to report in relation to this work.

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