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Common infectious and parasitic diseases as a cause of seizures: geographic distribution and contribution to the burden of epilepsy

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ABSTRACT

This educational review article aims to provide information on the central nervous system (CNS) infectious and parasitic diseases that frequently cause seizures and acquired epilepsy in the developing world. We explain the difficulties in defining acute symptomatic seizures, which are common in patients with meningitis, viral encephalitis, malaria, and neurocysticercosis, most of which are associated with increased mortality and morbidity, including subsequent epilepsy. Geographic location determines the common causes of infectious and parasitic diseases in a particular region. Management issues encompass prompt treatment of acute symptomatic seizures and the underlying CNS infection, correction of associated predisposing factors, and decisions regarding the appropriate choice and duration of antiseizure therapy. Although healthcare provider education, to recognize and diagnose seizures and epilepsy related to these diseases, is a feasible objective to save lives, prevention of CNS infections and infestations is the only definitive way forward to reduce the burden of epilepsy in developing countries.

Key words: acute symptomatic seizure, epileptogenesis, meningitis, encephalitis, treatment

Learning objectives and competencies for the International League Against Epilepsy (ILAE) curriculum

- 1.1 Demonstrate a working knowledge of etiologies for focal and generalized epilepsies in children and adults.
- 1.1.4 Describe the common infectious and parasitic causes of epilepsy, including geographical impact (*e.g.*, bacterial, fungal, viral, parasites).
- 3.0 Pharmacological treatment.
- 3.1 Demonstrate up-to-date knowledge about the range of pharmacological treatments for epilepsy.
- 3.1.5 Demonstrate knowledge about antiseizure medications (ASMs) and interactions (*e.g.*, enzyme induction, *etc.*) for ASM/ASM and ASM/concomitant medication (*e.g.*, oral contraceptives, treatment for TB, HIV, *etc.*)

Infectious and parasitic diseases of the CNS frequently cause seizures and epilepsy in endemic countries [1]. They are particularly prevalent in resource-limited countries, such as sub-Saharan Africa, where they cause epilepsy in 26% of affected individuals [2]. However, these diseases have no fixed boundaries with increasing migration, travel trade, and globalization. Infectious diseases are caused by microorganisms, protozoans, fungi, bacteria, viruses, and prions transmitted between people or between people and animals. Malaria, for example, is a vector-borne disease (*Anopheles* mosquitoes) caused by a parasitic protozoan (mainly *Plasmodium falciparum* and *P. vivax*); severe malaria is predominantly caused by *P. falciparum*. Parasitic infestations and the invasion of complex organisms, such as insects and worms, may be zoonotic infestations transmitted by animals to humans, such as the porcine tapeworm *Taenia solium* and neurocysticercosis.

Not all seizures associated with infectious and parasitic diseases are epilepsy

Infectious and parasitic diseases may cause insult-associated, provoked, acute symptomatic seizures (ASyS), defined as those "in close temporal relationship with an acute CNS insult, which may be metabolic, toxic, structural, infectious or due to inflammation" [3]. These seizures also include those associated with concomitant active infectious and parasitic diseases, however, there are significant difficulties in defining them in this etiological group of epilepsies. While for stroke or traumatic brain injury, ASyS are defined as those occurring within the first seven days after injury, for infectious and parasitic diseases due to acute and continued active brain inflammation, they may occur beyond seven days. Seizures sometimes take weeks or even months to resolve, especially when the onset of the illness is occasionally uncertain. This may be the case during the degenerative phase of neurocysticercosis, which may extend for three to six months; seizures occurring with viable parasites or calcifications are unprovoked [4]. This may also be the case for the cyclic fever of malaria, during the treatment of cerebral tuberculoma and brain abscess, and during acute infection or severe metabolic disturbances associated with HIV infection [3]. Therefore, in infectious and parasitic diseases, ASyS, either as isolated seizures or status epilepticus, have a variable underlying structural basis, course, and prognosis. To date, there are no adequate studies of etiology in the incident population of epilepsy in low- and middle-income countries (LMICs). Based on a series of all ages, in which 714 survivors of encephalitis and meningitis were analyzed, comprising 8,767 person-years, ASyS occurred in 44% of patients with encephalitis and 19% of those with bacterial meningitis. Seizures were focal in 74% of patients and bilateral tonic-clonic or of unknown onset in the remainder [5].

Development of epilepsy following acute symptomatic seizures

The overall risk ratio (RR) for developing epilepsy, defined as "an enduring predisposition of the brain to generate epileptic seizures" [6], compared to those without a CNS infection, was 6.9 [5]. The increased incidence of unprovoked seizures was highest during the first five years after the CNS infection and remained elevated over the next 15 years of follow-up. Overall, the reported risk of late unprovoked seizures in population-based cohorts of cerebral infection survivors from developed countries is estimated at 7-8% and much higher in resource-poor countries [7]. The type of infection and presence of ASyS greatly influences the risk of epilepsy, which is higher in patients with encephalitis (RR=16.2) than meningitis (RR=4.2). The presence of ASyS was shown to be a strong predictor of developing epilepsy over a period of 20 years; patients who had viral encephalitis and bacterial meningitis showed higher rates of developing epilepsy with ASyS than without ASyS (22% and 13% versus 10% and 2.4%, respectively) [5]. In a cohort of 147 patients with acute encephalitis followed for 2-15.8 years [8], 21% developed epilepsy after cerebral infection, of whom 10% were pharmacoresistant (more common [33%] in those with herpes simplex encephalitis). Status epilepticus was the only independent predictor of pharmacoresistance. Further predictors of pharmacoresistance in epilepsy after cerebral infections include focal seizures, intensive care admission, three or more antiseizure medications (ASMs), epileptiform discharges on EEG, T2/ FLAIR hyperintensity of the mesial temporal structures, and gadolinium enhancement on MRI [9]. Infections or infestations of the CNS are associated with factors related to the structural, immune, metabolic, and even genetic etiology of epilepsy. For most of them, the latent period, defined as the interval between the presumed infectious epileptogenic insult and the occurrence of late unprovoked seizures, is unpredictable. It will depend on etiology, severity, location of the insult, genetic background, epigenetic changes, and comorbidities. Infectious and parasitic diseases of the brain present an opportunity to study inflammatory pathways and conceptualize, test, and validate novel therapies to interfere with these pathways, thereby halting epileptogenesis and improving overall outcomes [10].

The present review aims to highlight common infectious and parasitic conditions that present with ASyS and epilepsy.

Common infectious diseases as an etiology of epilepsy according to geographic areas

Despite methodological differences among studies, there is a much higher incidence of epilepsy in LMICs (139 per 100,000 population) than in high-income countries (49 per 100,000 population) [1]. However, the average age-adjusted prevalence of epilepsy (8.5 per 1,000 people) in developing countries is similar to that in developed countries. This has been attributed to the higher mortality associated with epilepsy in developing countries, where approximately 80% of the world's people with epilepsy live. Of the 125,000 deaths related to epilepsy in 2016, estimated by the Global Burden of Epilepsy Report, 81% occurred in LMICs [11, 12]. CNS infectious and infestations were the most common causes cited for the higher incidence of seizures in these countries, where diseases such as cysticercosis, tuberculosis, and acquired immunodeficiency syndrome are endemic. The climate between the Tropic of Cancer and the Tropic of Capricorn (*i.e.*, the "tropics"), where 40 of the 50 million people with epilepsy live, half of them children, is especially conducive to neglected tropical diseases [12]. These are historically overlooked diseases, endemic in many resource-poor populations and developing countries, where poor sanitary conditions, inadequate nutrition, and a lack of access to necessary public health and health care systems for treatment predispose to these diseases. Awareness of these epilepsy etiologies, their geographical distributions (*table 1*), and their burden could help clinicians formulate differential diagnoses and health providers prioritize resources towards appropriate/control measures [7].

The exact mechanisms underlying the pathogenesis of CNS infections or infestations are incompletely understood but partially related to the pathogen, the degree of host inflammatory response, and cortical involvement.

Bacterial infections as a cause of seizures/epilepsy

Bacterial infections of the CNS are a highly crucial global health issue because of the high level of associated morbidity and mortality [13]. Almost any CNS bacterial infection can result in ASyS and subsequent risk of acquired epilepsy [14–16]. Key moderators in amplifying the risk of development of epilepsy are the age at the time of infection as well as the presence of a family history of epilepsy, alluding to

▼ **Table 1.** Predominant geographic distribution of some common central nervous system infectious and parasitic agents.

Infectious/parasitic disease	Causative organism	Geographic distribution	Comment
Malaria	*Plasmodium falciparum, malariae, vivax, ovale, knowlesi*	Sub-Saharan Africa, South East Asia, Latin America	The most common and fatal parasitic disease worldwide. *Plasmodium falciparum* is dominant in Africa, and *Plasmodium vivax* outside Africa
Japanese encephalitis	Japanese encephalitis virus (genus *Flavivirus*, family *Flaviviridae*)	India, China, Japan, South East Asia, the eastern Mediterranean region, Papua New Guinea, Australia	The most common cause of viral encephalitis worldwide. The virus continually spreads across geographical regions
Neurocysticercosis	*Taenia solium*	Latin America, India, China, South East Asia, some parts of Africa	Probably the most widely prevalent and well known for its association with seizures and epilepsy
Acquired immunodeficiency syndrome	Human immunodeficiency virus (HIV- genus *Lentivirus*, family *Retroviridae*)	Sub-Saharan Africa, Central Asia, Latin America, Eastern Europe	There are also variations within countries
Tuberculosis	*Mycobacterium tuberculosis*	India, China, South East Asia, sub-Saharan Africa, Latin America	Coinfection with HIV increasing

the significant role that genetic factors and brain maturation contribute in this regard [15, 16].

Bacterial infections can involve varied sections of the CNS, but majorly the meninges or cerebral parenchyma, leading to different clinical and pathological manifestations, depending on the area of the brain that has been infected, the age of the patient, virulence of the bacterial agent, as well as the severity of the infection [17, 18]. Three major infectious syndromes are defined according to the site and nature of the inflammatory reaction, namely: meningitis, abscesses, and encephalitis. However, the infectious syndromes of meningitis and brain abscesses are the most common clinical presentations of bacterial infections of the CNS, both of which are associated with the development of epilepsy and will be the focus of this section.

Nonetheless, a diagnosis of encephalitis should be considered in any patient presenting with a new-onset seizure or focal neurological deficit accompanied by fever, headache, altered mental status, or behavioral changes [17].

Bacterial meningitis

Bacterial meningitis continues to be a major problem in many areas of the world, both in developed and underdeveloped countries, with diverse etiological factors that vary by age group and geographical area [19]. It is estimated that over 2.5 million new cases of bacterial meningitis (excluding tuberculous and cryptococcal meningitis) occur globally each year [20]. Whereas bacterial meningitis occurs worldwide, Africa leads as the most affected continent, especially in the "Meningitis Belt" that extends from Senegal to Ethiopia and Somalia [21]. The classic signs and symptoms include sudden fever, severe headache, a stiff neck, photophobia, nausea, and vomiting. However, in children, especially neonates, non-specific signs and symptoms such as poor feeding, lethargy, irritability, apnea, or apathy may feature. The percentage of patients with seizures who suffer from acute bacterial meningitis varies from 17 to 47% [22–24].

The vast majority of bacterial meningitis is caused by three main agents: *Neisseria meningitides, Streptococcus pneumoniae, and Haemophilus influenzae*. However, due to the introduction of conjugate vaccines to *H. influenzae* type b (Hib) and *S. pneumoniae* in many countries, there has been a shift in the causes of meningitis to other bacteria such as Group B *Streptococcus* and *Escherichia coli* [25]. In view of the changing pathogen demographics following the advent of vaccines against these agents, the average age of a patient with meningitis has increased from 15 months of age in 1986 to 35 years in recent times [18].

The specific pathogens that cause bacterial meningitis also vary depending on the age group and the individual's host immune response [18]. In children during the neonatal period (newborn to 29 days), the key pathogens are aerobic Gram-negative bacilli, including *Escherichia coli*, Group B-hemolytic streptococci, *Listeria monocytogenes*, and *Klebsiella* species, among others. On the other hand, during childhood and adolescence, *N. meningitides* and *S. pneumoniae* play a major role in etiology [17].

Among adults, *S. pneumoniae* is the most important pathogen, with the highest risk notably seen in persons with sinusitis, mastoiditis, chronic otitis, CSF leaks, sickle cell disease, pneumococcal pneumonia, asplenia as well as those with alcohol addiction. In the elderly population, *L. monocytogenes* and Gram-negative bacilli (most often *E. coli*, *Klebsiella spp*., or *Enterobacter spp*.) are the most common pathogens. Moreover, *Staphylococcus aureus*, *Staphylococci epidermidis* (particularly in patients with CSF shunts), and aerobic Gram-negative bacilli (*Pseudomonas aeruginosa*) are common pathogens causing meningitis often secondary to head trauma and/or following neurosurgical procedures [17].

Bacterial meningitis is associated with significant morbidity with mortality rates ranging from 13 to 27% [26].

Brain abscesses

A systematic and meta-analytic review estimated the global population affected by intracranial abscesses to be 1,088,237 persons annually, with a higher incidence reported in immunocompromised populations [27].

Clinical signs and symptoms of patients with brain abscesses may vary depending on the location of the abscess, the virulence of the pathogenic microorganisms, and the immune response of the host. There are marked variations in clinical symptoms and signs, however, the most common symptoms include fever, headache, changes in mental status and behavior, and nausea and vomiting. Focal neurological deficits and other signs of a space-occupying lesion may also be present depending on the location of the abscess, including signs and symptoms of raised intracranial pressure. Seizures as the presenting symptom have been reported to occur in 25-34% of patients [28, 29].

Cerebral abscesses are usually associated with predisposing factors such as sinusitis, otitis media, dental abscesses, congenital heart disease with right-to-left shunt, and pulmonary infection [14, 15], and sometimes, an etiology cannot be identified. *Streptococcus* and *Staphylococcus* species are implicated in the vast majority of bacterial brain abscesses, although anaerobic bacteria such as *Bacteroides*, *Fusobacterium*, *Prevotella,* and *Actinomyces* species are also key

pathogens, and about a quarter of cases are due to polymicrobial agents. Among those severely immunocompromised (e.g., with HIV infection, transplantation), CNS tuberculosis, *Nocardia*, and fungal (e.g., *Aspergillus spp., Candida spp., Cryptococcal neoformans, Histoplasma capsulatum*) and parasitic (e.g., *Toxoplasma gondii*) infections are commonly associated with brain abscesses [17], especially when multiple brain abscesses are detected on imaging [30]. Significant mortality from brain abscesses has also been recorded with figures as high as 40%, but this has since decreased to 10% from the year 2000, owing to advances in diagnostic imaging and management strategies [31].

The proposed pathophysiology: how bacterial pathogens invade the CNS

In general, the CNS is extremely resistant to infection by bacterial pathogens due to a combination of protective effects from its bony structures (skull and vertebral column), the meninges, and the blood-brain barrier (BBB). Although the precise mechanisms by which most bacteria gain access to the cerebral spinal fluid (CSF) remains controversial, it is now known that intracellular and extracellular bacteria have developed different strategies to evade the host defense systems [32]. However, once the infection has occurred, the CNS tends to be more vulnerable than most other tissues, as the host defense mechanisms typical of other areas of the body do not provide an adequate response in the CNS to prevent bacterial replication and progression of the disease process [33].

Meningitis may result from the direct spread of pathogens from adjacent body structures to the brain, such as the paranasal sinuses, middle ear, and mastoid sinuses, as well as through a retrograde route via representative veins from the face or scalp. Direct implantation of pathogens may follow from congenital defects such as myelomeningoceles, a trauma in penetrating injuries, and compound skull fractures or ensue from surgical procedures as well as invasive diagnostic and therapeutic interventions. CNS tuberculosis is usually caused by *Mycobacterium tuberculosis* which reaches the brain by the hematogenous route from the lungs [15].

The source of infection is unknown in about 25% of brain abscesses. Nevertheless, brain abscesses are generally a secondary infection from extracerebral primary sources that involve the CNS through either hematogenous or immediate spread from adjacent structures. Abscesses secondary to hematogenous spread from a distant focus account for about 20-25% of cases. In adults, the most common primary sources are pulmonary infections such as bronchiectasis and lung abscesses, followed by dental infections, while in children, the most common primary source is congenital cardiac disease with a right-to-left shunt due to paradoxical emboli [31].

Abscesses secondary to the contiguous spread of a local infection into the brain may account for about 20% of cases [32]. In children, sinusitis, acute and chronic otitis, and mastoiditis are important sources, while in adults, sinusitis and osteomyelitis of the adjacent bony skull structures are common sources [31].

The direct implantation of microorganisms during penetrating head trauma and postsurgical procedures may also result in brain abscesses, with a reported incidence of about 2% to 37% [32, 33].

The interplay between bacterial infectious organisms and the manifestation of epilepsy, and its consequences

Access of the infectious agent to the cerebral cortex, with or without damage to it, is necessary for seizures to develop. Once the pathogenic bacterial organisms evade the host's defense mechanisms, they are spread via the blood or from infectious foci in the vicinity of the brain, to ultimately invade the CNS, resulting in inflammation of the meninges, increased BBB permeability, CSF pleocytosis, and infiltration of the nervous tissue. In an attempt to ward off the attack, the host mounts a massive systemic inflammatory response that leads to leukocyte extravasation into the subarachnoid space, increased CSF outflow resistance, and brain edema. Systemic inflammation may also result in the development of vasculitis, cerebral venous thrombosis, and secondary ischemia [34]. Furthermore, the proinflammatory bacterial compounds can stimulate the immune cells within the brain parenchyma, particularly microglia, leading to neuronal injury [35]. Neuronal injury is facilitated by the release of oxygen free radicals, cytokines, excitatory amino acids, activation of transcription factors, and proteases.

All the above-mentioned brain modifications occur during the latency period (between infection and onset of ASyS), with resultant molecular and structural reorganization, and epigenetic reprogramming, which may eventually cause spontaneous recurrent epileptic seizures (*i.e.*, epilepsy).

Following the latency period (which may range from several weeks to up to nine years during the acute illness), focal seizures, which are often pharmacoresistant, will develop in 5-10% of meningitis survivors. The majority of unprovoked seizures occur within five years of the meningitis episode and tend to be recurrent [35]. Whereas the occurrence of ASyS and the later development of epilepsy in survivors of

bacterial meningitis are well known, the complete characterization of seizure risk according to the infective agent is still an area that requires more research [14].

Bacterial meningitis caused by any one of the three main agents (*N. meningitides, S. pneumoniae,* or *H. influenzae*) is postulated to generate a purulent exudate that colonizes the subarachnoid space. This state, coupled with a direct effect of toxin production, leads to inflammatory reactions, which are likely to be contributory to ASyS and later epilepsy development.

For brain abscesses, up to a quarter of cases will present with ASyS. A high proportion of survivors, especially those following temporal abscesses, will later develop focal epilepsy, which is usually highly refractory to treatment and often associated with other neurological disabilities [14, 15].

In CNS tuberculosis, about 20% of people develop seizures [14] as a result of cerebral vasculitis and infarction, especially in young children and in people co-infected with HIV. Focal seizures may also occur as an end result of tuberculomas, identified as ring-enhancing lesions on neuroimaging. Regardless of whether CNS tuberculosis takes the form of subacute meningitis or intraparenchymal tuberculomas, all manifestations are associated with a high risk of seizures which are usually pharmacoresistant [14, 15]. CNS tuberculosis is highly associated with epilepsy, irrespective of whether or not tuberculomas are apparent.

Risk factors for seizures/development of epilepsy

Early seizures (ASyS; provoked or insult-associated seizures), which occur at or soon after the time of the acute phase of meningitis, are not considered spontaneous seizures, since they are mechanistically different from those that result in significant chronic epilepsy. Early seizures, however, are a risk factor for the later development of epilepsy, although not all people with early seizures will develop late seizures, and not all of those with late seizures have early seizures [37].

The ASyS that occur during acute meningitis are highly associated with both late seizures and permanent neurological deficits. However, it should be noted that most children who have ASyS do not subsequently have permanent neurological sequelae, including epilepsy. Many of these ASyS may just be febrile seizures.

The probability of developing unprovoked seizures or epilepsy varies according to the etiological agent responsible for meningitis, and this probability appears to be higher for *Streptococcus pneumoniae* [35]. One hospital-based study noted that children with persistent neurological abnormalities other than sensorineural hearing loss demonstrated an increased risk of at least one late unprovoked seizure [37]. Other reported risk factors included EEG abnormalities, particularly focal slowing and sharp waves, and an initial CSF glucose concentration <20 mg/dL [38].

Other research findings show the risk of developing epilepsy due to bacterial infections is dependent on the individual's age, the virulence of the organism, accessibility to medical resources, presence of seizures during the acute illness, low CSF glucose on admission, and persistent neurological and EEG abnormalities [11]. The risk among children varies according to age group; neonates with Group B streptococcal meningitis have a greater risk of developing epilepsy relative to those with *Escherichia coli*. On the other hand, in older children and adults, pneumococcal meningitis is associated with a greater risk of developing epilepsy [39]. Additional risk factors, especially in low-resource settings, include late recognition and presentation for appropriate care at the health facility and inadequate treatment [40].

Bacterial meningitis may also induce status epilepticus, a life-threatening neurological and medical emergency associated with high mortality. This oftentimes arises if there is a persistence of fever and refractory seizures even after antibiotics and aggressive ASM therapy, which may indicate either antimicrobial resistance or underlying immunodeficiency [41].

Epilepsy occurrence following a brain abscess is relatively variable; in one European study, 34% of patients with brain abscesses developed epilepsy, whilst in an Asian study, only 6.4% developed epilepsy, mainly within the first three years following diagnosis [42]. There are limited comparable studies from Africa.

Knowledge gaps related to bacterial pathogens and future perspectives

Bacterial infections of the CNS are an important cause of both ASyS and later epilepsy, as well as other neurological disabilities, especially in resource-poor settings where there is the greatest burden of acute and long-term infection-related seizures. However, neither the exact mechanisms by which most bacteria gain access to the CSF nor the underlying mechanisms leading to the development of neurological sequelae such as epilepsy are entirely understood. Furthermore, the full characterization of seizure risk according to the infective agent has not been described.

Studies that can establish accurate estimates of the whole spectrum of attributable risk factors for epilepsy and shed more light on understanding the pathogenesis of CNS disease associated with these

infections, in particular, the molecular basis of all epilepsies, are urgently needed.
Other key research priority areas include: enriched tool development for the assessment of neurological, cognitive, and mental health impairments; other interventions for preventing other bacterial infections such as vaccines; more effective methods to treat and prevent nervous system sequelae; and establishing evidence-based research to implement known effective interventions for improved management of cases. Research in these areas, coupled with efforts to implement evidence-based technologies and therapies, may have significant effects on reducing the morbidity resulting from these infections.
Future prospective studies will be needed to establish whether early administration of other promising adjuvant therapies would reduce the risk of subsequent development of unprovoked seizures/epilepsy.

Viral diseases as a cause of seizures/epilepsy

Viral encephalitis

Viral encephalitis refers to the most acute inflammation of the brain, specifically caused by viral infection [43]. The condition should be differentiated based on indirect involvement of the brain, as well as strong inflammatory underpinnings attributed to indirect, often delayed, effects of the virus, *e.g.*, acute disseminated encephalomyelitis and post-viral autoimmune encephalitis [44]. Although viral encephalitis is relatively frequent and widespread, its symptoms and signs are non-specific and the diagnostic yield is poor [43]. Fever arouses suspicion of viral encephalitis, sometimes with skin rash and other constitutional symptoms along with varying degrees of alteration in sensorium and orientation and seizures. These symptoms can plausibly be caused by other conditions, such as bacterial and parasitic infections and immune-allergic disorders of the brain. The confirmation of the diagnosis is based on diverse investigations including CSF examination following a lumbar puncture, EEG, MRI, and serological, virological, and molecular diagnostic methods. Currently, confirmatory evidence is mostly based on viral amplification techniques (*e.g.*, polymerase chain reaction) using the CSF. Still, it eludes the diagnosis in nearly a half of cases [45]. Metagenomic next-generation sequencing of the CSF is an upcoming diagnostic tool, but its availability is restricted [46]. Reliance on serological examinations, *e.g.*, a rising titer in the serum or the presence of virus-specific IgM antibodies in the CSF, and direct virological examination of brain tissue may be less informative.

The list of viruses that can cause encephalitis is long (*table 2*), however, the viruses can be divided into those causing epidemic encephalitides with characteristic geographical predilections and those causing sporadic encephalitis [45, 47, 48]. Examples include herpes simplex viruses (HSV), type 1 and 2, cytomegalovirus, and human herpes viruses, type 6 and 7. Overall, Japanese B encephalitis is the most common cause of viral encephalitis. The infection is endemic in most of South and Southeast Asia.
Many affected individuals have seizures during the active phase of viral encephalitis. The proportion of ASyS varies according to the viral agent. Seizures are very common and occur in 40-60% of the cases with HSV encephalitis. Seizures were reported in nearly 70% of a small series of 14 patients with Eastern equine encephalitis, nearly all those with Venezuelan equine encephalitis, and 24% with Nipah encephalitis [49, 50]. The proportion of those with ASyS with other geographically-specific encephalitides, including Western equine encephalitis, La Crosse encephalitis, St. Louis encephalitis, West Nile encephalitis, and Japanese B encephalitis, is low, probably less than 10% [51–56]. Some studies of series of hospitalized patients with Japanese B encephalitis have reported higher frequencies of seizures, and these appear to be more common in children and in those with other features associated with raised intracranial pressure [56].
The true incidence of ASyS in patients with viral encephalitis can perhaps be gauged in population-based studies. Moreover, hospital-based studies might underestimate the incidence of seizures as many of these seizures are non-convulsive or purely electrographic. Continuous or prolonged EEG monitoring is credibly indicated in hospitalized cases of viral encephalitis with altered sensorium. The diagnostic yield of this investigation might be inordinately high. At times, non-convulsive status epilepticus is uncovered, which might have been otherwise missed. The identification of lateralized periodic discharges (LPDs) is common during the acute phase of viral encephalitis and LPDs (previously PLEDs- periodic lateralized epileptiform discharges) denote acute focal brain damage. Currently, however, there is no standardized agreement on care for managing patients with LPDs [43, 57, 58]. There is agreement that treatment is required if associated with overt clinical or electrographic seizures.
Late unprovoked seizures following an episode of acute viral encephalitis are quite common and denote epilepsy. In a seminal study with rigorous back-dated follow-up, the incidence of late unprovoked seizures following an episode of viral encephalitis was increased 16-fold [5]. The risk increased to 22-fold when early seizures or ASyS complicated the acute viral encephalitis episode. Furthermore, the risk was

▼ **Table 2.** Viruses causing encephalitis and their geographic correlates and propensity to cause seizures.

Virus	Geographical predilection	Incidence of acute symptomatic seizures	Reference
Sporadic encephalitis			
Herpes simplex virus Type 1 & 2	None	>60%	Riancho *et al.*, 2013 [57]
Human herpes viruses Type 6 & 7	None	NA	
Cytomegalovirus	None	NA	
Epidemic or endemic encephalitis			
Japanese B encephalitis	South Asia, Southeast Asia	10-50%	Misra and Kalita, 2001 [55]; Solomon *et al.*, 2002 [56]
Eastern equine encephalitis	American East Coast and Gulf	70%	Silverman *et al.*, 2013 [49]
Western equine encephalitis	California	10%	Kokernot *et al.*, 1953 [51]
La Crosse encephalitis	California	80%	Teleron *et al.*, 2016 [53] Chun, 1983 [54]
Venezuelan equine encephalitis	South & Central America	98%	CDC, 1995 [50]
St Louis encephalitis	Midwest US	10%	Venkat *et al.*, 2020 [52]
West Nile encephalitis	Throughout the US	10%	Venkat *et al.*, 2020 [52]

high during the first five years; it decreased thereafter but remained high for nearly 20 years.

Specific viral infections are probably associated with different risks of late unprovoked seizures. The risk of late unprovoked seizures is highest for viral encephalitides with HSV [57]. It is also markedly elevated in survivors of La Crosse encephalitis [53, 54]. The risk of epilepsy with encephalitides involving the subcortical structures, *e.g.*, Western equine encephalitis, Japanese B encephalitis, and Nipah encephalitis, are probably lower. Other risk factors include, but are not limited to, the occurrence of early seizures and the identification of MRI and EEG abnormalities [58]. In general, the occurrence of acute symptomatic status epilepticus increases the risk of late unprovoked seizures in patients with acute brain insults [59], though this has not been specifically demonstrated after viral encephalitis [58].

The control of late unprovoked seizures following viral encephalitis can be problematic but has not been systematically studied. Pharmacoresistant epilepsy is common and may indicate surgical treatment. In an early study of surgical approaches to pharmacoresistant epilepsy following viral encephalitis and bacterial meningitis, the latter was often associated with unilateral mesial temporal sclerosis, which led to good postoperative seizure outcomes [60]. On the other hand, viral encephalitis was frequently associated with neocortical localizations, often multiple or bilateral mesial temporal sclerosis, which precluded surgical treatment. At the same time, the location and distribution of epileptogenic substrates after viral encephalitis presaged poor outcomes, with postoperative seizure freedom rates of about 30% [60]. More experience and perspective have been gained since this initial small study, and invasive recording and stereo-EEG have been frequently employed in the lead-up to surgery in post-encephalitic pharmacoresistant epilepsy [61]. Various surgical approaches have been employed in post-encephalitic epilepsies, including anteromesial temporal resection, electrocorticography-guided focal neocortical resection, temporoparietal disconnection, peri-insular hemispherectomy, corpus callosotomy, and vagus nerve stimulation [61]. The surgical outcome remains unsatisfactory, and the chances of post-operative seizure freedom do not exceed 30% [62].

HSV encephalitis is typically thought to be an acute one-stage disorder and an initial precipitating insult for chronic post-encephalitic epilepsy. However, this one-to-one relationship might be blurred in some cases and prolonged smoldering inflammation has been detected in histopathological specimens from temporal lobectomies for post-encephalitic epilepsy [63]. These cases of smoldering inflammation are distinctly different from the finding of HSV genome as well as HHV-6B virus DNA in the absence of any inflammation (or prior encephalitic episodes) from temporal lobe specimens of individuals with pharmacoresistant mesial temporal lobe epilepsy [64, 65]. These findings have fueled the speculation that herpes viruses might be a potential etiology for mesial temporal sclerosis but should be construed in the light of the neurovirulent potential of human herpes viruses. Herpes viruses are well known to be present but dormant in human CNS tissue, and may be activated at older ages [66]. On a related note, epilepsy surgery has been reported to reactivate herpes simplex infection in the brain, and this finding has led to the administration of prophylactic acyclovir during surgery for post-encephalitic pharmacoresistant epilepsy [67].

Recently, humankind has been facing the challenge of coronavirus disease 19 (COVID-19). This viral agent, named severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), emerged from Wuhan, China, and rapidly spread worldwide. However, the prevalence of ASyS caused by SARS-COV-2 (<1%) was lower than that related to other similar viruses (ranging from 2.7 for SARS to 8.6% for Middle East respiratory syndrome). On the other hand, the increase of seizures in people with epilepsy during this pandemic setting ranged from 8% to 35%, regardless of the presence of COVID-19. At present, epilepsy should not be considered a risk factor for COVID-19, as there is a lack of strong evidence to support this statement. There is also a lack of data to affirm the incidence of epilepsy as a neurological complication of SARS-COV-2 infection, as well as the clinical profile related to this type of virus and its control with ASMs [68]. Concerning status epilepticus, a recent systematic review showed that it could be a neurological manifestation of COVID-19, occurring before or throughout the active infectious phase. However, the causal relationship between SARS-COV-2 infection and status epilepticus is still uncertain [69].

Parasitic diseases as a cause of seizures/epilepsy

Parasitic diseases affecting the CNS remain an important source of morbidity and mortality worldwide, mainly in LMICs; nevertheless, sporadic cases also occur in non-endemic areas because of an increase in international travel and migration. Parasites can be broadly classified into single-celled organisms (*i.e.*, protozoa) or multicellular helminths (*i.e.*, metazoa) (*table 3*). Protozoa have the ability to multiply in an immunosuppressed environment, which explains why most of the severe parasitic opportunistic infections in patients with HIV are caused by protozoan parasites. Helminths include flatworms (trematodes and cestodes) and roundworms (nematodes). Parasitic diseases are caused by diverse organisms with an array of vectors or intermediate hosts, modes of transmission, and endemic regions or geographic distributions (*table 3*). The most common parasitic infections of the CNS are cysticercosis, toxoplasmosis, and echinococcosis; less frequent infections are malaria, toxocariasis, and onchocerciasis.

Clinical description of the main parasitic diseases of the central nervous system

Clinical manifestations are highly heterogeneous (*figure 1*). Crossover between signs and symptoms, such as seizures, meningoencephalitis, and focal neurologic deficits, occurs with many parasitic diseases, thus making the differential diagnosis challenging.

- ***Neurocysticercosis***

Clinical manifestations are heterogeneous and depend mainly on the localization of cysts and immune response by the host. Seizures, headaches, focal deficits, and cognitive abnormalities are the most frequent manifestations of cysts in the brain parenchyma [70]. On the contrary, extraparenchymal cysts can be life-threatening due to hydrocephalus related to intraventricular cysts, arachnoiditis or ependymitis [71]. New diagnostic criteria for neurocysticercosis have recently been validated [72]. An attribute of the new criteria is that they permit the distinction between parenchymal and extraparenchymal neurocysticercosis (*table 4*).

- ***Echinococcosis (hydatidosis)***

E. granulosus and *E. multilocularis* cause cystic echinococcosis and alveolar echinococcosis, respectively. The infection may be primary or secondary to the spontaneous or traumatic rupture of a primary cerebral cyst or the embolization of cardiac cysts [73]. Cysts may remain asymptomatic until large enough to cause a mass effect. Cerebral lesions occur in 1% to 4% of individuals with cystic echinococcosis, with non-specific clinical findings related to space-occupying lesions, increased intracranial pressure, and seizure activity [74].

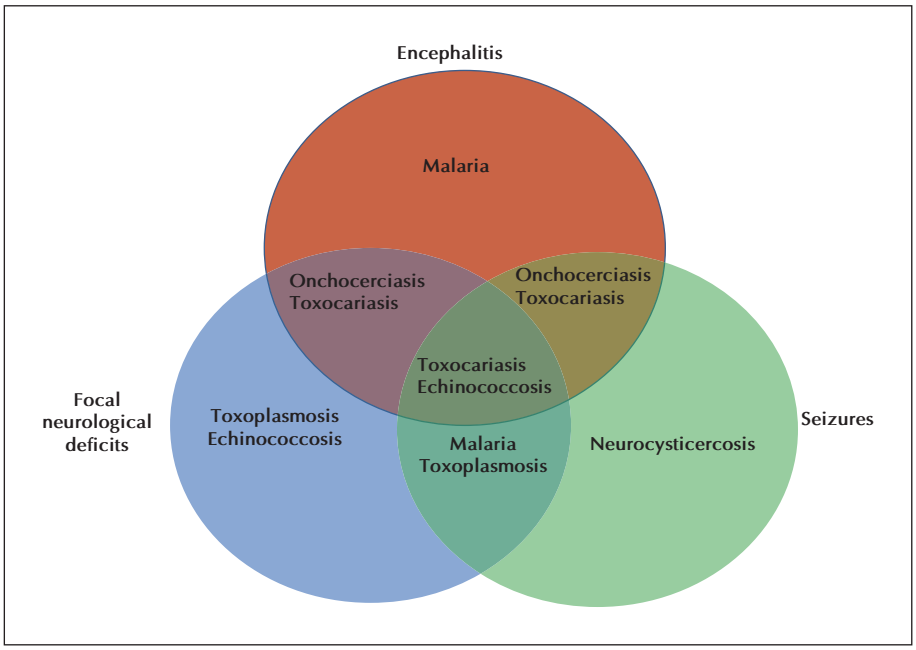
▼ **Table 3.** Common parasitic diseases related to seizures and epilepsy.

Parasitic disease	Causative organism	Vector / intermediate host	Mode of transmission	Endemic region	Treatment
Metazoa (Helminths)					
Taeniasis/ Cysticercosis	*Taenia solium* (Cestode, flatworm)	Pigs, humans	Fecal-oral, ingestion of eggs from human feces	Latin America, Africa, Asia	Albendazole or praziquantel, with corticosteroids
Echinococcosis (Hydatidosis)	*Echinococcus granulosus* *Echinococcus multilocularis* (Cestode flatworm)	EG*: Sheep, goats, cattle, pigs EM**: Small mammals (rodents and lagomorphs)	Ingestion of contaminated soil, water or food	Middle East, Europe, Pacific, Latin America; Inuit populations in North America	Albendazole or mebendazole (alone or with surgery)
Toxocariasis	*Toxocara canis, Toxocara cati* (nematode, roundworm)	Cats, humans	Fecal/oral, contaminated soil	Worldwide	Albendazole or mebendazole, with corticosteroids
Onchocerciasis (Filariases)	*Onchocerca volvulus* (Nematode, roundworm)	Vector borne, Blackflye Similium	Insect bite	West and Central Africa, parts of Central and South America	Ivermectin Doxycycline
Protozoa					
Malaria	*Plasmodium falciparum*	Vector borne, Anopheles mosquito	Insect bite	Tropics from Sub-Saharan Africa, Latin America, Asia and Oceania	IV artesunate IV quinine dihydrochloride or quinidine gluconate + doxycycline, tetracycline, or clindamycin
Toxoplasmosis	*Toxoplasma gondii*	Cats, intermediate hosts in nature (including birds and rodents)	Ingestion of oocysts (cat feces) or tissue cysts (undercooked meats), from mother to fetus	Worldwide, the greatest burden in sub-Saharan Africa and Asia	Sulfadiazine + pyrimethamine with leucovorin Clindamycin + pyrimethamine Trimethoprim +sulfamethoxazol

*EG: *Echinococcus granulosus*
**EM: *Echinococcus multilocularis*

• ***Toxocariasis***
There are three main syndromes associated with toxocariasis: visceral larva migrans, which encompasses diseases associated with major organs; covert toxocariasis, which is a milder version; and ocular larva migrans, in which the pathological effects on the host are restricted to the eye and the optic nerve [75]. CNS infestation may present with seizures, eosinophilic meningitis, optic neuritis, and meningomyelitis.

• ***Onchocerciasis***
Also named "river blindness", onchocerciasis leads to symptoms such as severe itching, bumps under the skin, and blindness. It has also been proposed to be a potential risk factor for epilepsy due to the high prevalence of onchocerciasis in areas with a high



■ **Figure 1.** Parasitic diseases of the central nervous system with overlapping clinical manifestations.

prevalence of epilepsy. Analytical work on this association has produced conflicting results, perhaps related to confounders or a lack of standardized methods [76]. Onchocerciasis has been suggested to cause nodding syndrome, an epileptic encephalopathy characterized in children in Africa, that manifests with a unique epilepsy type characterized by a repetitive short loss of neck muscle tone resulting in a forward bobbing of the head, not attributable to any other neurological or psychiatric condition, often in association with progressive neurocognitive impairment and physical decline [77].

• ***Malaria***

This is the most common tropical parasitic disease worldwide. It affects primarily African children and Asian adults, with the vast majority (greater than 90%) of cases occurring in children five years old or younger. Cerebral malaria is caused by *Plasmodium falciparum* and may result in acute encephalopathy with fever and seizures, which may be fatal or lead to polymorphic neurological sequelae [78]. The pathophysiology of brain involvement is multifactorial but is related to the degree of parasitemia, sequestration of schizonts in the brain venules, and the resulting vascular and perivascular damage [7]. Proposed mechanisms of injury include anoxia, vascular leakage, parasite toxin, and metabolic derangements.

• ***Toxoplasmosis***

Toxoplama gondii cysts may develop in any tissue, but most commonly develop in the brain, retina, skeletal muscle, and cardiac muscle. Rupture of the cysts releases free tachyzoite, which causes acute illness [79]. Fever, rash, lymphadenopathy, and eye disturbances are typical in the early stages. When lesions occur in the CNS of immunocompromised patients, fever, headaches, confusion, and seizures are common, as well as ocular disease (retinochoroiditis). Some infections are subclinical, and 20% of HIV-infected patients with toxoplasmosis develop encephalitis. The disease may also be transmitted transplacentally and have destructive effects on the fetal brain [80]. Seizures, microcephaly, and chorioretinitis have been noted in most of these cases [81].

Diagnosis of parasitic diseases

As for cerebral malaria and toxoplasmosis, direct visualization of the parasite is definitive. In many parasitic diseases, however, this is not a feasible option. Therefore, developing specific and sensitive serodiagnostic and molecular biological (polymerase chain reaction [PCR]) assays will complement and confirm clinical examination. Parasite DNA can originate from both the live and dead organisms, and thus, a positive PCR is not necessarily definitive proof of

▼ **Table 4.** New diagnostic criteria for symptomatic neurocysticercosis.

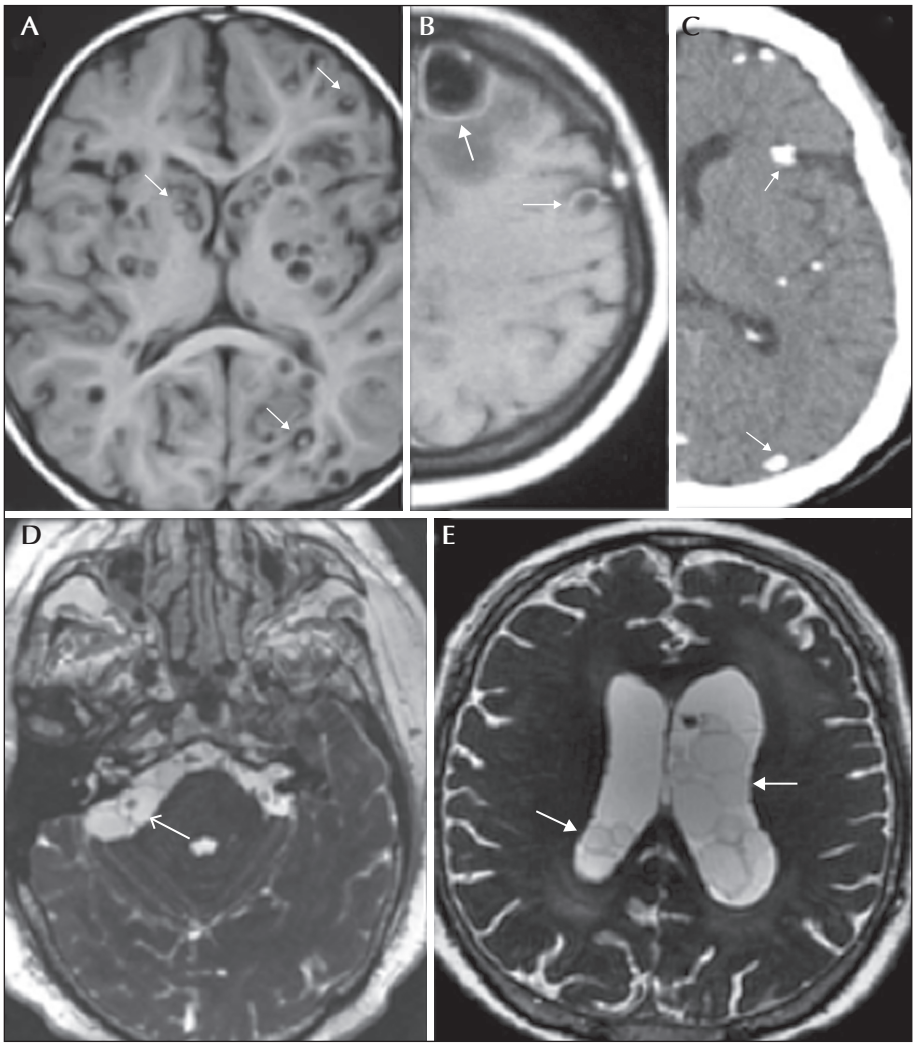
1. Parenchymal neurocysticercosis
Definitive parenchymal neurocysticercosis*, one of the following:
1. Parenchymal cyst with pathological diagnosis
2. Single or multiple active parenchymal cysts, with at least one cyst with scolex on CT or MRI
3. Multiple parenchymal vesicles without scolex associated with at least one of the following:
a. Seizures: focal or bilateral tonic-clonic
b. Positive serum or CSF immunological test (ELISA, EITB)
4. =Any combination of the parenchymal cysticercus in different evolutive stages: vesicular with or without scolex, degenerative (colloidal or nodular), and calcified
Probable parenchymal neurocysticercosis, one of the following:
1. Single parenchymal calcification or vesicle (without scolex) or degenerating cyst(s), establishing differential diagnoses with other etiologies, associated with at least two of the following:
a. Seizures: focal or generalized tonic-clonic
b. Subcutaneous or muscle cysts: location confirmed by biopsy
c. Positive serum or CSF immunological test (ELISA, EITB)
d. Plain X-ray films showing "cigar-shaped" calcifications
e. Individual who lives or has lived in or has traveled frequently to endemic countries
2. Multiple parenchymal calcifications in an individual who lives or has lived in or has traveled frequently to endemic countries and in whom the clinical state excludes other etiologies of calcifications
2. Extraparenchymal neurocysticercosis (intraventricular/basal subarachnoid)
Definitive extraparenchymal neurocysticercosis, one of the following:
1. Extraparenchymal cyst with pathological diagnosis
2. One or more extraparenchymal cysts on MRI specific sequences with scolex on at least one of them
3. One or more extraparenchymal cysts on MRI specific sequences without scolex associated with at least two of the following:
a. Hydrocephalus
b. Inflammatory CSF
c. Positive CSF immunological test (ELISA, EITB)
d. Presence of single or multiple calcifications or parenchymal vesicular or degenerative cyst
3. Definitive parenchymal and extraparenchymal neurocysticercosis
Combination of the above definitive parenchymal and definitive extraparenchymal criteria

*Parasites located in the subarachnoid space of the convexity include parenchymal parasites [72].

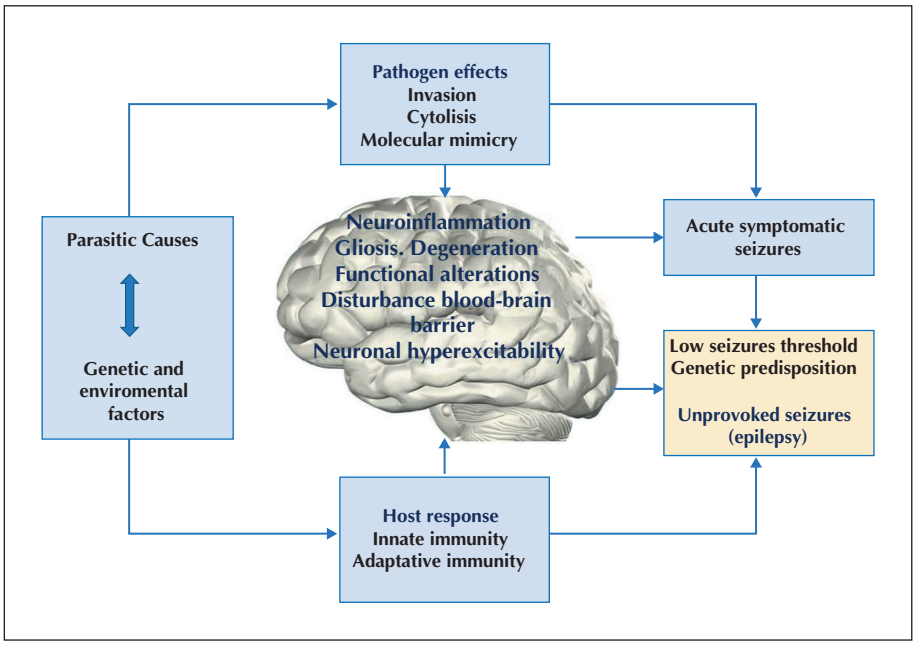
viable parasite infection [80]. Like malaria, the "gold standard" for diagnosing toxoplasmosis is the detection of the parasite by microscopy. Complementary techniques include detecting circulating *Toxoplasma gondii* antigens, anti-toxoplasma antibodies, and a variety of PCR protocols [79]. It is highly important to confirm toxoplasmosis in neonates, which is achieved by detecting IgM antibodies in CSF, typically using either the indirect fluorescein antibody test or the Sabin-Feldman dye test [80]. Diagnosis of cerebral echinococcosis follows the common pattern of serological confirmation subsequent to the observation of neurological symptoms. Diagnostic testing for anti-parasite antibodies using parasite extracts or a western blotting protocol has been described [83]. For cerebral toxocariasis, it is preferable to confirm

diagnosis by detecting antibodies to egg antigens or secretions of infective larvae, preferably in CSF.

Neuroimaging studies (MRI and CT) play an essential role in early diagnosis, however, there is a wide range of neuroimaging findings associated with parasitic diseases of the CNS, often with considerable overlap, which makes the determination of a specific diagnosis difficult. Therefore, correlation with laboratory tests, especially CSF analysis, is important in establishing a definitive diagnosis. Parasitic diseases in the CNS develop inflammation revealed by hypercellularity and as a consequence of edema. Cellular malfunction leads to the development of a breakdown in the blood-brain barrier, which is evident by imaging studies. Neuroimaging is especially useful in the diagnosis of neurocysticercosis since it permits visualization of the parasite stage, as well as the number and localization of lesions [72]. Specifically, imaging procedures allow visualization of vesicular, colloidal, granular-nodular, and calcified phases of neurocysticercosis in the CNS (*figure 2*). Extraparenchymal neurocysticercosis is more difficult to detect by imaging because the attenuation and signal intensity of the cyst's content are similar to that of CSF, the cystic wall is usually not detected, there is no enhancement after intravenous contrast administration, and the cysts frequently lack a scolex (*figure 2*).



■ **Figure 2.** Imaging of parenchymal and extraparenchymal neurocysticercosis. (A) T1-weighted MRI showing viable multiple parenchymal cysts with scolex (arrows). (B) T1-weighted MRI showing degenerative-colloidal cysts (arrows). (C) CT showing multiple parenchymal calcifications (arrows). (D) 3D MRI sequence (FIESTA) showing cysticerci at the cerebellopontine cistern (arrow). (E) 3D MRI sequence (FIESTA) showing cysts inside the ventricles (arrows).



■ **Figure 3.** Flow diagram summarizing epileptogenic mechanisms associated with parasite infections.

Hydatid cysts in imaging studies appear as large, well-defined, smooth, cystic lesions that are spherical or oval, usually with no surrounding edema. The cyst contents typically have CSF-like density on CT, and CSF-like signal characteristics on MRI. On post-contrast images, a thin rim of enhancement may be seen. The presence of a daughter cyst within a cystic lesion is considered pathognomonic of an echinococcus cyst [77]. Neuroimaging in patients with toxoplasmosis commonly shows multifocal abscesses with a preference for the basal ganglia. Most lesions show enhancement, often in a ring-like pattern [70]. MRI of toxocariasis shows non-specific, circumscribed, multifocal lesions in the brain white matter, with contrast enhancement [82]. Imaging findings in cerebral malaria include cerebral edema, cortical and subcortical ischemic lesions, and multiple petechial hemorrhages. Validated diagnostic criteria for CNS infections in general have not yet been properly established worldwide (except for neurocysticercosis), which represents a gap in daily medical practice and especially in research. Thus, we encourage further studies with this goal in mind.

The interplay between parasitic diseases and the manifestation of seizures/epilepsy, and its consequences

Most parasites known to infect the brain have been implicated in causing seizures. Neurocysticercosis is most clearly recognized as a frequent cause of seizures and epilepsy. Recent studies of other parasitic diseases, such as cerebral malaria and onchocerciasis, yield novel insight into the pathogenesis of parasite-associated epilepsy.

The interplay between parasites and CNS and how these may lead to epilepsy are summarized in *figure 3*. The immune mechanisms involved in these neurological disorders include increased cytokine levels, immune cell infiltration into the CNS, and autoantibodies [80]. During an initial brain insult, proinflammatory cytokines (mainly IL-Iβ, IL-2, and IL-6) produced by glial cells and neurons may cause cerebral injury [83]. The liberated cytokines also activate astrocytes and microglia resulting in proinflammatory cytokine-induced alterations in blood-brain-barrier integrity and subsequent neuronal hyperexcitability [84]. Several processes occur, including brain neuronal hyperexcitability facilitated by both N-methyl-D-aspartate (NMDA) receptor and other glutamate-mediated mechanisms, neuronal loss, and gliosis. These processes may ultimately result in recurrent unprovoked epileptic seizures [7]. A multifactorial concept for epileptogenesis in people with neurocysticercosis was proposed [70], based on the triad of epileptogenic abnormality, seizure threshold, and precipitating factors, leading to a cascade of inflammatory and immunological mechanisms that may contribute to triggering seizures. Individuals with a low seizure threshold and

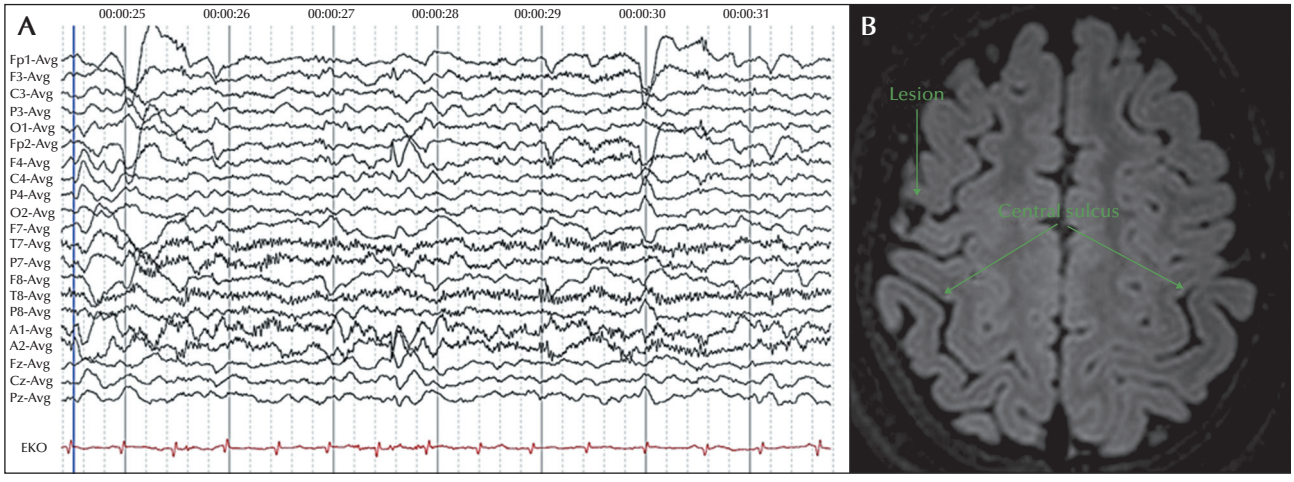
precipitating factors may have ASyS due to parasitic epileptogenic lesions and seizures that recur over time due to a genetic predisposition that maintains a low threshold, *i.e.*, epilepsy. However, in the absence of genetic predisposition associated with a low threshold, seizures may not recur, and the individual may not develop epilepsy.

Treatment of parasitic infections of the central nervous system

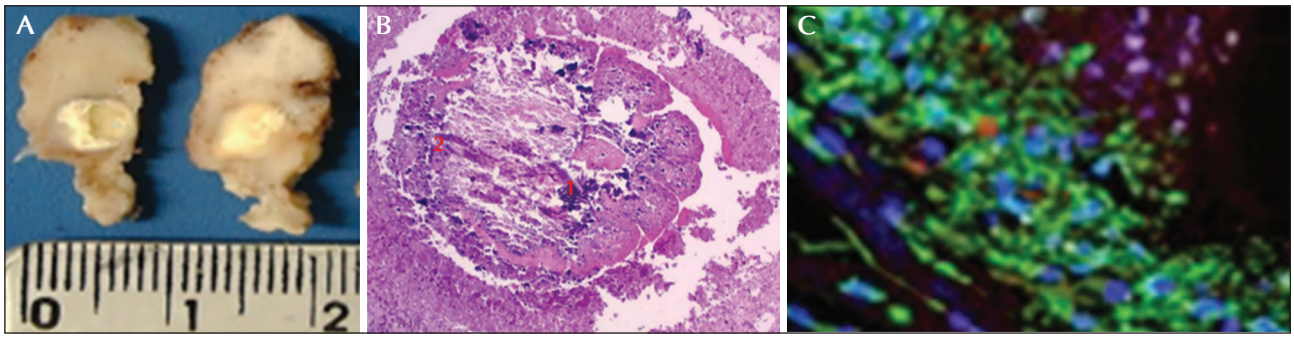
Medical treatment involves parasiticides to kill the parasite and adjunctive care to prevent or treat complications related to infiltration of the parasite, such as ASMs. In addition, surgical treatment might involve cyst removal or treating complications of the parasite such as hydrocephalus. Anthelmintic medications are widely used (*table 3*); these include two medications in the benzimidazole class, albendazole and mebendazole, which are widely used for the treatment of nematode and cestode infections. Ivermectin is used to treat a variety of nematode and ectoparasite infections and praziquantel is used to treat trematode and some cestode parasites. Treatment of cerebral malaria requires IV antimalarials; artesunate performs better than quinine. The treatment of parasiticides for CNS parasitic diseases has been reviewed elsewhere [80], however, to date, accurate doses and well-defined duration of treatment have not been evaluated based on well-conducted clinical trials.

Case 1

A six-year-old, right-handed girl, who lived in a rural area in Brazil, was evaluated in a pediatric epilepsy outpatient clinic. She started to have seizures three years ago, which gradually became more frequent. By the time of this evaluation, seizures occurred in sleep and wakefulness. Sometimes the patient was aware of her surroundings during the seizures. The seizures were short with a frequency varying from 3 to 30 per day. There were periods when the girl did not have any seizure and others when they recurred, several on the same day. Throughout her life, she has taken multiple ASMs (valproic acid, carbamazepine, clobazam, topiramate, ethosuximide, levetiracetam and cannabidiol) with maximum tolerated doses, and has tried a ketogenic diet. On the neurological examination, no focal deficits were found and all cognitive functions were normal (scores in the lower/middle range). The routine EEG exhibited very frequent bilateral frontal interictal epileptiform activity, with predominance on the right (*figure 4A*). Her brain MRI revealed a single nodular calcification located in the right frontal gyrus (*figure 4B*). As this patient had pharmacoresistant epilepsy, she was considered for epilepsy surgery. Therefore, a presurgical multidisciplinary evaluation was performed, registering three types of seizures during VEEG: myoclonic-tonic, asymmetric tonic, and behavioral arrest seizures. Subsequently, a resection of the calcified lesion (*figure 5A*) was performed, revealing a necrotic cysticercus (*figure 5*B) with microglial activation (*figure 5C*), which confirmed the etiological



■ **Figure 4.** (A) Case 1. The patient's interictal EEG reveals the predominance of epileptiform activity on the right frontal region due to higher amplitude seen on electrode F4 (display settings: average longitudinal montage, 7-µV/mm sensitivity, 70-Hz high-frequency filter, 0.5-Hz low-frequency filter, and 60-Hz notch filter). (B) A hypointense signal is seen in the right mid-frontal gyrus on an SWI (susceptibility-weighted imaging) sequence in calcified lesions; the central sulcus is a landmark to localize the frontal lobe.



■ **Figure 5.** (A) Case 1. After epilepsy surgery, a calcified lesion was resected and the macroscopic examination revealed a cysticercus within the lesion. (B) Hematoxylin and eosin-stained brain specimen showing the scolex of *Taenia solium* (1), as well as the necrotic vesicle wall (2). (C) This immunofluorescence analysis evaluated the presence of a calcium-binding protein for microglia (in blue) in the region of *Taenia solium's* wall with necrosis (in green), showing brain inflammation that is considered a predisposition factor for the chronic epileptogenic process.

diagnosis of neurocysticercosis infection. After epilepsy surgery, the child remained seizure-free, without any focal deficit or worsening in her cognitive performance [108].

Risk factors for seizures/development of epilepsy

Some studies, mainly in rural communities of LMICs, have independently reported a proportion of epilepsy cases attributable to parasitic diseases, varying widely from one study to another, ranging from 5.7% to 39.3% (*table 5*). These conflicting results are perhaps related to confounders (other infections) or a lack of standardization in the methods. Odds ratios, comparing risks of epilepsy in persons seropositive for parasitic disease antibodies, were reported from 1.69 to 2.8 (*table 6*). One study reported that cortical lesions due to alveolar echinococcosis (hazard ratio= 29.740) were significantly associated with the development of epilepsy. Two studies compared the risk of epilepsy in persons with and without evidence of cerebral malaria, reporting an odds ratio for malaria hospitalization of 4.68 and for cerebral malaria diagnosis of 3.3 (*table 6*). The risk of epilepsy associated with onchocerciasis was assessed in a study examining onchocerciasis subcutaneous nodules (rate ratio = 1.68) and a study comparing onchocerciasis skin snip biopsies (odds ratio = 2.63).

The risk factors mentioned above for parasitic diseases are based mainly on cross-sectional studies or retrospective case-control studies using prevalent cases that have provided some evidence of an association between exposure to parasitic infestations and epilepsy. This does not necessarily imply causation since other factors, such as poor access to health facilities and conditions associated with poverty, may be common to both conditions. There is a lack of prospective longitudinal studies to examine the incidence of epilepsy following infection or a reduction in epilepsy following control of the parasitic diseases. We currently do not know the risk factors for the development of epilepsy following ASyS due to CNS infectious and parasitic diseases [7].

Knowledge gaps and future perspectives

Parasitic diseases of the CNS can be life-threatening but are often preventable and treatable, however, clinical outcomes largely depend on early diagnosis and treatment. Anti-parasite antibodies are synthesized soon after host invasion, and so their detection is still the most frequently employed diagnostic tool. However, it should be taken into account that detection is not definitive proof of a current, viable infection as antibodies can persist for months, even years, after eliminating the parasite. Neuroimaging studies (CT and MRI) play an important role in early diagnosis, however, there is a wide range of neuroimaging findings in CNS parasite infections, often with considerable overlap, which makes diagnosis difficult. Prospective cohort studies are needed to assess the association of the different phases of the parasite, the role of precipitating factors in the development of seizures, and the potential genetic predisposition to epilepsy. In this context, the use of ILAE guidelines for epidemiological studies to standardize concepts of classification of seizures and epilepsy is mandatory [1].

▼ **Table 5.** Percent of attributed etiologies based on studies of people with seizures and epilepsy by country.

Country (Author, year)	Etiological category	Percentage
Ndimubanzi, ϕ 2010 [85]	Neurocysticercosis	29% (23-35)
India Singh, 2020 [86]	Neurocysticercosis	11.7%
China Li, 2021 [74]	Echinococcosis	20%
China Chen, 2018 [87]	Echinococcosis	6.7%
Iran Alizadeh Khatir, 2021 [82]	Toxocariasis	39.3% (29-50)
Egypt Eraky, 2016 [88]	Toxocariasis	5.7%
Congo, Vieri, 2021 * [89]	Onchocerciasis	18.5%
Cameroon, Morin, 2020 [90]	Onchocerciasis	47.6%
Benin, Thierry, 2020 [91]	Malaria	31.7%
Kenya Serem, 2015 [92]	Malaria	33%
Mexico Alvarado-Esquivel, 2018 [93]	Toxoplasmosis	10%
Egypt Eraky, 2016 [88]	Toxoplasmosis	20%

ϕ Review paper, includes many countries.
*This study also reports Taeniasis/cysticercosis at 8.2%.

Future studies should meet all the following basic methodological requirements:
- an adequate study design and use of validated surveys in community-based studies;
- neuroimaging, molecular (PCR), and serological assays (Ag- ELISA and enzyme-linked immunoelectrotransfer blot assays) should be performed for all included participants;
- case-control studies with appropriate levels of exposure to parasites;
- adequate statistical power by selecting a sufficient number of people with epilepsy and controls;
- matching of controls by sex, age, location, and confounders.

This approach will facilitate our understanding of the epidemiological burden of CNS parasitic disorders in LMICs, considering that most of these diseases will not be eradicated in the short term; instead, their incidence will likely increase along with inequality, poverty, and associated socio-economic problems. More research on risk factors of epilepsy is needed, employing consistent definitions that describe the causality of parasitic diseases. This applies especially to LMICs, where large regions in the world are still represented by few studies and where risks may vary significantly according to local health care infrastructure, economies, culture, and technology.

Treatment of seizures and epilepsy

At the same time etiology is investigated, ASyS and status epilepticus associated with CNS infections and parasitic diseases are treated like other ASyS [11]. Caring for these patients requires an understanding of the basic factors that underlie human infectious and parasitic diseases. In sub-Saharan Africa, and other regions where malaria is endemic, malaria must be considered in any febrile patient with seizures, and blood films should be obtained to look for malarial parasites. In India, some regions of South America, and other South Asian countries, cysticercosis needs to be considered in an afebrile, otherwise, healthy person with new-onset focal seizures, and neuroimaging is warranted in all such individuals. Tuberculosis should be taken into consideration regarding a history of prolonged low-grade fever and systemic symptoms, particularly if there are associated neurological deficits [11]. There are three fundamental points that guide the treatment of these diseases.

1. Use of etiological treatment as early as possible

Early aggressive therapy of the underlying infection and its complications may prevent seizures and epilepsy. However, systematic studies to document this are not available. Early treatment of bacterial meningitis with appropriate antibiotics may reduce complications such as infarction, subdural empyema, or cerebral abscesses. The impact of antimicrobial therapy on immediate mortality and morbidity is unquestionable. However, its effect on long-term complications is less certain; it perhaps reduces the incidence of late seizures and epilepsy.

- ***Treatment of seizures and effect of antiparasitic treatment on seizure outcomes***

A recent Cochrane review [97] addressed the assessment of ASM effects on the primary and secondary

▼ **Table 6.** Comparative risks of seizures/epilepsy by parasitic disease.

Probable cause	Author	Study design	Locality	Number	Age	Risk factor	Metric	Finding (95% CI)
Neurocysticercosis	Ngugi, 2013 [93]	Meta-analysis*	Africa ϕ	1711	All	*T. solium* seropositivity	OR	1.98 (0.72-5.43)
Neurocysticercosis	Singh, 2012 [94]	Cross-sectional	Punjab, India	106	All	*T. solium* seropositivity	OR	2.8 (1.2-6.8)
Echinococcosis	Li, 2021 [74]	Retrospective	Tibet, China	97	All	*Echinococcus* seropositivity	HR	29.7 (p=0.006)
Echinococcosis	Mmbando, 2018 [73]	Cross-sectional	Mahenge, Tanzania	127	All	*Echinococcus* seropositivity	OR	1.96 (1.09-3.53)
Toxocariasis	Alizadeh Khatir, 2021 [82]	Case-control	Iran	94	All	*Toxocara* seropositivity	OR	2.38 (1.25-4.63)
Toxocariasis	Luna, 2018 [75]	Meta-analysis	Several countries ϕϕϕ	850	All	*Toxocara* seropositivity	OR	1.69 (1.42-2.01)
Onchocerciasis	Kaiser, 2011 [96]	Case-control	West Uganda	38	All	Onchocerciasis subcutaneous nodules	RR	1.68 (0.60-4.57)
Onchocerciasis	Mandro, 2018 [76]	Case-control	Congo	175	All	Skin snip biopsies	OR	2.63 (1.63-4.23)
Malaria	Thierry, 2020 [91]	Case-control	Parakou, Benin	41	<16	Malaria cerebral	OR	3.3 (2.3-4.8)
Malaria	Christensen, 2015 [78]	Case-control	Sub-Saharan Africa	1711	All	Malaria hospitalization	OR	4.68 (2.52-8.70)
Toxoplamosis	Alvarado-Esquivel, 2018 [79]	Case-control	Durango, Mexico	99	All	*T.gondii* seropositivity	OR	1.74 (0.60-4.99)
Toxoplamosis	Sadeghi, 2019 [81]	Meta-analysis	Several countries ϕϕ	3771	All	Toxoplasma seropositivity	OR	1.72 (1.37-2.16)

ϕ Includes: Kenya, South Africa, Uganda, Tanzania, Ghana;
ϕϕ Includes: Israel, Egypt, Mexico, Uganda, Turkey, USA, Iran, Sub-Saharan Africa;
ϕϕϕ Includes: USA, Italy, Bolivia, Turkey, Burundy, Tanzania.
OR: odds ratio; CI: confidence interval; RR: rate ratio; HR: hazard ratio.

prevention of seizures in people with neurocysticercosis. It concluded that there is currently no evidence available regarding the duration of ASM treatment required. Since most patients with parasitic diseases present with seizures (*figure 1*), a logical question is whether antiparasitic therapy also improves seizure outcome, an effect possibly mediated through the resolution of parasites. The effect of antiparasitic therapy with albendazole on seizure outcome in patients with multiple cysticerci cysts has been explored in landmark RCTs in Peru [98] and Ecuador [99]. Both trials found no significant difference in the risk of seizure during long-term follow-up after treatment (*i.e.*, seizure recurrence), however, neither

trial was powered to test this association. Studies regarding the long-term prognosis of seizures due to CNS parasitic diseases are very scarce. However, evidence suggests that the prognosis of patients with parenchymal neurocysticercosis is usually good, in terms of recurrence of seizures over time [4]. Overall, in patients with ASyS, ASMs should be maintained during the period of local inflammatory activity, and they can be withdrawn once the follow-up imaging shows resolution.

2. Avoid interactions between therapeutic agents

Interaction between ASMs and anti-infective therapy can significantly alter the level of each medication, leading to either decreased efficacy or toxicity. It is, therefore, important for physicians to be aware of such interactions [100]. This is particularly important in individuals with HIV, in whom antiretroviral agents have considerable interactions with ASMs. Some of the newer ASMs, such as levetiracetam, gabapentin, pregabalin and lacosamide, have very few interactions and may be preferred. ASMs and agents used in the treatment of infectious and parasitic diseases that may give rise to important and clinically significant interactions include:

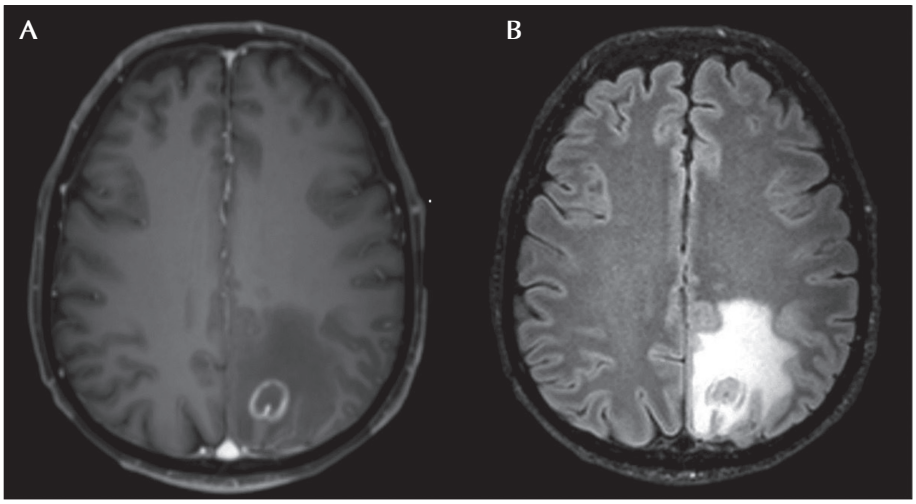
- **Antibiotics.** Carbapenem antibiotics, such as imipenem, meropenem, ertapenem and panipenem, can cause a prominent, clinically significant decrease in the serum concentrations of valproic acid; potent inhibitors of CYP3A4 such as macrolide antibiotics, erythromycin, clarithromycin, and triacetyloleandomycin may increase carbamazepine serum levels. Rifampicin, a strong enzyme inducer, can reduce lamotrigine by about 50%, as well as lacosamide concentrations [100].
- **Antivirals.** Strong enzyme-inducing ASMs (carbamazepine, phenytoin, phenobarbital, and primidone) reduce antiretroviral agents; the consequences of loss of efficacy due to this enzyme induction can be severe and even fatal. Due to its enzyme-inhibiting activity, valproic acid may increase the serum concentrations of zidovudine and lopinavir. The antiretroviral combination of lopinavir/ritonavir reduces serum lamotrigine concentrations by about 50% and phenytoin concentrations by about 30%, atazanavir/ritonavir reduces serum lamotrigine levels by about 30%, and efavirenz reduces serum carbamazepine concentrations by 27% on average [100].
- **Other agents.** Strong enzyme-inducing ASMs (carbamazepine, phenytoin, phenobarbital, and primidone) also reduce albendazole, chloramphenicol, doxycycline, efavirenz, indinavir, itraconazole, lopinavir, metronidazole, nevirapine, posiconazole, praziquantel, rifampicin, ritonavir, saquinavir, voriconazole and corticosteroids [100].
- **Parasiticide interactions.** Strong enzyme-inducing ASMs are also potent inducers of CYP isoenzymes, including 3A and 1A [101]. CYP 3A isoenzymes are involved in the metabolism of both albendazole and praziquantel, and 1A isoenzymes are involved in the metabolism of praziquantel. In addition, first-generation ASMs have high plasma protein binding capability, similar to both parasiticides [102]. Drug-drug interaction studies have shown a significant pharmacokinetic interaction between ASMs and antihelminthic agents. Some studies have reported that albendazole and praziquantel plasma concentrations are significantly reduced by the coadministration of ASMs [102]. The use of newer ASMs, which do not induce CYP enzymes and exhibit a lower level of plasma protein binding, may warrant further evaluation for use during parasiticide treatment, to assess whether their use has any differential effect on parasite eradication.

Case 2

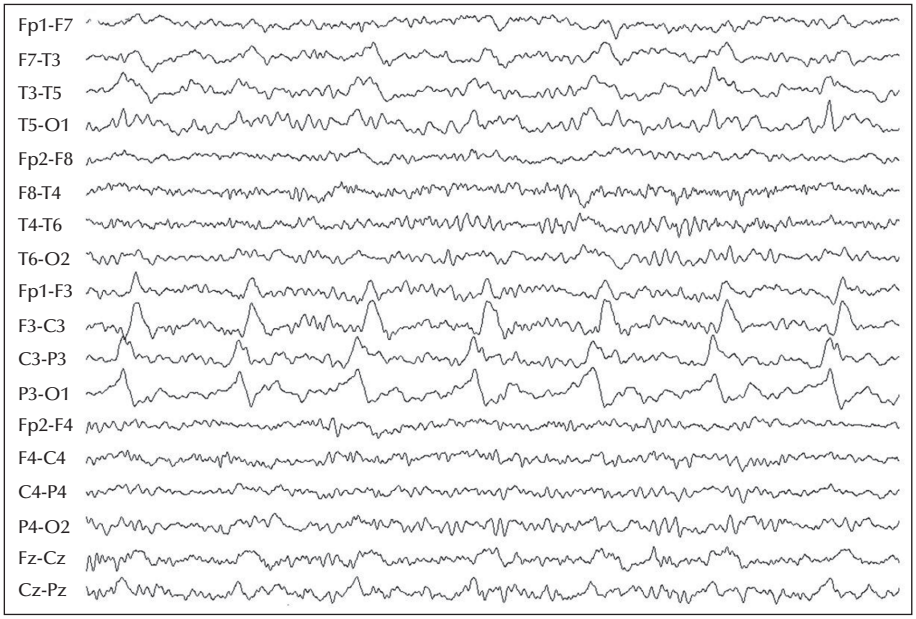
A 48-year-old man presented with a history of two events characterized by sudden disorientation and inability to move the right side of the body, lasting a few minutes. Physical examination revealed right homonymous hemianopia, mild right hemiparesis, and Gerstmann syndrome (acalculia, finger agnosia, agraphia, and left-right confusion). In addition, he presented with signs of oral moniliasis. In the hospital, he exhibited a bilateral tonic-clonic seizure of unknown onset.

An HIV test was positive, with a viral load of 581,263 copies and a CD4 count of 250 cells/mm^3. Serology for anti-toxoplasma IgG antibodies was positive. Brain MRI showed a left parietal subcortical lesion with intense ring enhancement and an eccentrically located enhancing mural nodule, compounding the eccentric target sign, suggestive of CNS toxoplasmosis (*figure 6*). The EEG demonstrated continuous LPDs in the left hemisphere, with maximum voltage on the rolandic (C3) and parietal (P3) electrodes, which were monomorphic, without spatiotemporal evolution or any plus modifier, and showed a frequency of 0.5-1 Hz (*figure 7*). This LPD pattern was interpreted as being associated with the acute cerebral lesion and could imply a propensity to generate seizures.

The patient underwent empirical treatment for CNS toxoplasmosis with sulfadiazine and pyrimethamine. Concurrently, valproic acid was initiated and rapidly titrated to 1,000 mg/day (20 mg/kg). The team chose valproic acid because it was the available medication that could be rapidly titrated and did not induce the metabolism of other required medications. He gradually improved during the following weeks. EEG after one week showed resolution of the LPD pattern with intermittent slow activity over the left hemisphere. MRI after two weeks revealed a significant reduction of the lesion and edema. The patient has remained seizure-free since then.



■ **Figure 6.** Case 2. Brain MRI of the patient with CNS toxoplasmosis. (A) Axial T1 with gadolinium showing the eccentric target sign. (B) Axial T2 FLAIR demonstrates the lesion with prominent surrounding vasogenic edema.



■ **Figure 7.** Case 2. EEG of the patient with CNS toxoplasmosis reveals continuous lateralized periodic discharges in the left hemisphere. EEG was acquired with a sample rate of 512 Hz using the international 10-20 electrode placement system (display settings: bipolar longitudinal montage, 7-µV/mm sensitivity, 70-Hz high-frequency filter, 0.5-Hz low-frequency filter, and 60-Hz notch filter).

3. Prevent the development of epilepsy following ASyS. Are ASMs contributory?

Since seizure generation during most CNS infections and parasitic diseases is associated with an inflammatory response, the possibility of reducing seizures with the use of anti-inflammatory agents can be hypothesized. The effect of anti-infective treatment on subsequent epilepsy cannot be studied in a controlled manner because most anti-infective therapies constitute the standard of care. Hence, denying such treatment is ethically unacceptable.

Early administration of adjunctive corticosteroids has been shown to reduce mortality, severe hearing loss, and neurological sequelae in HIV and pneumococcal meningitis cases in developed countries. However, this is not so in developing countries [103]. Corticosteroids are advocated for tuberculous meningitis as they reduce death and disability [104]. However, whether corticosteroids play a role in reducing seizures and epilepsy in patients with bacterial or tuberculous meningitis has not been specifically studied. The adjunctive use of dexamethasone in patients with malaria was not found to be of any benefit, and in one trial was associated with increased complications [105]. A network meta-analysis that assessed seizure recurrence in patients with solitary cysticercus granuloma found that the combination therapy of albendazole and corticosteroids reduced the risk of seizure recurrence compared with conservative treatment (limited to the treatment of symptoms), however, the differences were not statistically significant [106]. Other anti-inflammatory agents such as pentoxifylline, and immunomodulatory agents such as intravenous immunoglobulins are being explored.

Duration of ASM treatment

The duration of ASM therapy has been debated, and no evidence-based recommendations exist [11]. In acute bacterial meningitis, early seizures do not require long-term ASMs, however, those occurring late (after four days) are often associated with an underlying complication and tend to recur. ASMs are often continued for a few months in such cases [11]. In HIV, ASyS have a high tendency to recur, hence ASMs are continued for a long time [11]. Unprovoked seizures and epilepsy require long-term ASMs. In neurocysticercosis, the conventional practice was to use ASMs for a two-year seizure-free period. However, a randomized study did not find any difference in seizure recurrence between those who received ASMs for one year versus those who received ASMs over a two-year seizure-free interval. Seizure recurrence was associated with persistence or calcification of lesions and an abnormal EEG [107]. Hence, one-year ASM therapy seems adequate for children in whom the lesions disappear; those with persistent lesions require a longer duration of ASMs. The duration of ASM therapy depends on several factors and needs to be individualized. Some patients may develop pharmacoresistant epilepsy and may be excellent surgical candidates, particularly those with a history of meningitis or encephalitis in early childhood, hippocampal sclerosis on MRI, as well as a history, seizure semiology, and EEG findings compatible with the diagnosis of a mesial temporal lobe epilepsy syndrome [9]. More challenging are patients with neocortical/extratemporal lobe epilepsies post cerebral infection. Finally, patients with a severe hemispheric injury with contralateral hemiparesis are candidates for hemispheric disconnection [9].

Conclusion

Deaths in epilepsy patients in LMICs are largely preventable by improving access to care, including diagnosis and treatment, and promoting adherence to therapy through healthcare provider education to recognize and diagnose seizures and epilepsy. Poor sanitation, a lack of clean water, crowded living conditions, and a lack of vaccination contribute to the disproportionate burden of epilepsy in these countries. Preventive CNS infections and parasitic disease programs should be the leading priority for health care authorities. ■

Key points

- Despite the much higher incidence of epilepsy in low- and middle-income countries than in high-income countries, the prevalence of epilepsy is similar, probably due to higher mortality associated with seizures in developing countries.
- In infectious and parasitic diseases with continued active brain inflammation, acute symptomatic seizures may take weeks or even months to resolve.
- Fever associated with recent-onset seizures in a traveller who has been to sub-Saharan Africa country compels an investigation for malaria.
- The type of infection and presence of acute symptomatic seizures are strong predictors of developing epilepsy, particularly in cases of viral encephalitis.
- The average age of patients with meningitis has increased from 15 months to 35 years due to vaccination against *H. influenzae* and *S. pneumoniae*.
- When multiple brain abscesses are shown on imaging, the most common agents are fungi and parasites such as *Toxoplasma gondii*.

- At least 50% of patients with viral encephalitis have seizures, and the risk of epilepsy increases 22-fold when early or acute seizures complicate the acute viral encephalitis episode.
- Evidence of multiple parenchymal vesicles with or without scolex, associated with focal or bilateral tonic-clonic seizures, is sufficient for a definitive diagnosis of neurocysticercosis.
- In a patient with epilepsy taking valproic acid, who received a carbapenem antibiotic and entered status epilepticus in the intensive care unit, serum levels of valproic acid should be evaluated, as serum levels may have been dramatically reduced.
- The anthelminthics, albendazole and praziquantel, may not be effective in patients treated with enzyme-inducing ASMs.

Supplementary material.
Summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

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TEST YOURSELF

(1) Which of the following CNS infections is associated with the greatest risk of late unprovoked seizures?

A. Bacterial meningitis without early seizures
B. Viral encephalitis with early seizures
C. Viral encephalitis without early seizures
D. Aseptic meningitis

(2) A four-year-old baby is admitted to the emergency unit with a history of poor feeding, lethargy, and irritability. Following the history-taking and examination, you make a diagnosis of meningitis and conduct a lumbar puncture. Which of the following is the most likely organism to be identified based on the cerebral spinal fluid laboratory analysis?

A. *S. pneumoniae*
B. Group B *Streptococci*
C. E. coli
D. L. monocytogenes

(3) In a patient with a prior history of viral meningoencephalitis, which of the following statements is correct?

A. An unprovoked seizure occurring six months after the resolution of the meningoencephalitis should be considered as acute symptomatic seizure
B. This patient has the same probability of developing epilepsy as that of the general population
C. The risk of developing epilepsy is higher if the agent was herpes simplex virus
D. The risk of developing epilepsy is lower if the patient presented with acute symptomatic seizures

(4) Which of the following statements is correct regarding parasitic infections?

A. There are no adequate studies of etiology regarding the incident population of epilepsy in low- and middle-income countries
B. Clinical manifestations of brain parasitic diseases are clearly identifiable
C. The "gold standard" for diagnosing brain parasitic diseases is imaging (computed tomography or magnetic resonance imaging)
D. The risk factors for the development of epilepsy in patients with central nervous system parasitic diseases are well known

(5) Which of the following should be undertaken to prevent triggering epilepsy during the treatment of infectious diseases?

A. Perform the etiologic treatment with antihelminthic agents only after starting antiseizure medications
B. Choose medicines with interactions between antiseizure medications and antihelminthic agents
C. Try to prevent the development of epilepsy following acute symptomatic seizures
D. Use antiseizure medications as primary and secondary prevention of seizures in people with neurocysticercosis

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.