

Seizures and epilepsy in central nervous system infections

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INTRODUCTION

Infections are among the most common causes of seizures. All ages may have seizures due to infections ranging from toxoplasma in the newborn to the Creutzfeldt-Jacob disease in the elderly. Seizures may be the only presenting symptom of an infection such as neurocysticercosis or only one symptom of global central nervous system dysfunction, such as in subacute sclerosing panencephalitis and rabies. In this review, various viral and fungal infectious diseases of the central nervous system resulting in seizures and epilepsy are discussed.

EPIDEMIOLOGY

The frequency of epilepsy is greater in tropical than in developed countries. This may be due to increased risk associated with poor peri-natal care, head injury, and infectious diseases. Population-based pilot studies of small populations using a WHO protocol averaged rates of 18 per thousand population, higher than in developed countries where prevalence ranged from 2.7 to 8.0.¹ Poor sanitation, malnutrition and health care, drugs and substance abuse, prostitution and human immunodeficiency virus infection are all increasing in these countries and adding to the spectrum of tropical problems that may lead to epilepsy. Infections are important cause epilepsy in developing countries, the frequency of which may differ widely in different locations. Viral, bacterial, fungal and parasitic infections can result in epilepsy.

VIRAL DISEASES

Viral infection of the brain may cause either aseptic meningitis or encephalitis. The virus causing aseptic meningitis includes entero-virus (more common in developing countries because of faecal-oral transmission), mumps, arena viruses, herpes simplex type-2, varicella zoster and HIV.

Herpes encephalitis

Herpes simplex virus is a DNA virus that causes the most common form of sporadic fatal encephalitis in children older than six months and adults worldwide. Herpes simplex virus brain infections are divided into two groups: neonatal herpes simplex virus infection, which is caused by HSV-2, and herpes simplex encephalitis, which occurs in children and adults caused by HSV-1. Herpes simplex encephalitis has no pathognomonic clinical presentation but presents as focal encephalitis with malaise; focal seizures that may become generalized. Herpes simplex encephalitis produces dramatic electroencephalographic (EEG) focal temporal or lateralized polymorphic delta activity as the earliest changes.² CT and MRI reveal medial temporal involvement.

Japanese encephalitis

Japanese encephalitis is mosquito borne flavivirus, which is the most common cause of arboviral encephalitis worldwide. The illness occurs throughout Asia and seen more often in children than in adults. Convulsions may occur as part of severe encephalitis and, the mortality rates are high (20% to 40%). MRI shows thalamic and basal ganglia involvement (Figure 1). Neurologic sequelae are present in majority of survivors.³ Extra-pyramidal syndrome evolves during convalescence and this may include parkinsonism in some patients due to the involvement of substantia nigra (Figure 2).⁴ About 10% of the patients may show a bi-phasic illness pattern in which the seizures are more common during first or the acute phase of the illness.⁵

Rabies

Rabies, caused by a rhabdo-virus, presents approximately 30 days after contact with a rabid animal. a nonspecific prodrome of fever, headache, sore throat, and abdominal pain progresses to a hyperactive, hallucinatory stage

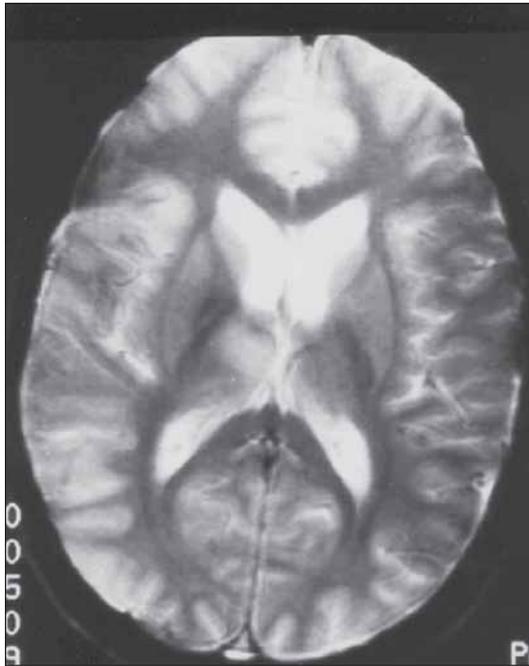


Figure 1. T2 weighted MRI of brain in Japanese encephalitis showing predominant involvement of basal ganglia.



Figure 2. T2 weighted MRI of brain in Japanese encephalitis showing predominantly involvement of substantia nigra in midbrain region.

followed by coma and death. Seizures occur in about 10% of patients.⁶ Without post-exposure immuno-prophylactic treatment and vaccination survival is rare.

Human immunodeficiency virus

Cytomegalovirus produces typical encephalitis with fever, headache and seizures. Cytomegalovirus can cause seizures in 4% to 11% of human immunodeficiency virus-infected patients.^{7,8} Considering together 276 patients described in four large series in human immunodeficiency virus, it was found that generalized convulsive seizures constitute 75% of attacks, with the remainder being partial seizures.⁷⁻¹⁰

PARASITIC DISEASES

Neurocysticercosis

Cysticercosis is a disease caused by the infection with the larval stage of the intestinal cystode *Taenia solium* that occurs when human or porcine become intermediate hosts. The parasite has marked tendency to infect muscle and the central nervous system where it produces a pleomorphic clinical disorder neurocysticercosis.

In many developing countries neurocysticercosis is the most common parasitic disease of the central nervous system and accounts for 10% of all acute neurological diseases.¹¹ There are wide variations of clinical manifestations of neurocysticercosis. These are consequence of inflammation around a cyst, space occupation and impedance to the flow of cerebrospinal fluid. Less commonly, there is meningeal or vascular inflammation. Epilepsy is the most common manifestation of neurocysticercosis, occurring in two-third of affected patients.¹² These may occur both when a cyst is degenerating, and around a chronic calcified lesion (Figure 3). In Mexico City, neurocysticercosis is the cause of seizures in 50% of adult onset epilepsy.¹³ Seizures in neurocysticercosis are generalized convulsive or simple partial with focal motor activity. Medina *et al.* in their series of 50 patients with epilepsy due to neurocysticercosis¹³, found that 72% had partial seizures. Del Brutto *et al.* studied clinical characteristics of 203 patients with epilepsy and neurocysticercosis and found generalized convulsive seizures in 38% and complex partial seizures in 2%. In that series, neurological examination was normal in 80%, focal deficits was seen in 16%, and papilloedema in 4%. Acute symptomatic seizures occur during the focal encephalitic illness caused by degenerating parasite but chronic epileptogenic focus that causes late epilepsy develops due to healing by peri-lesional gliosis.¹⁴ This gliosis has been found

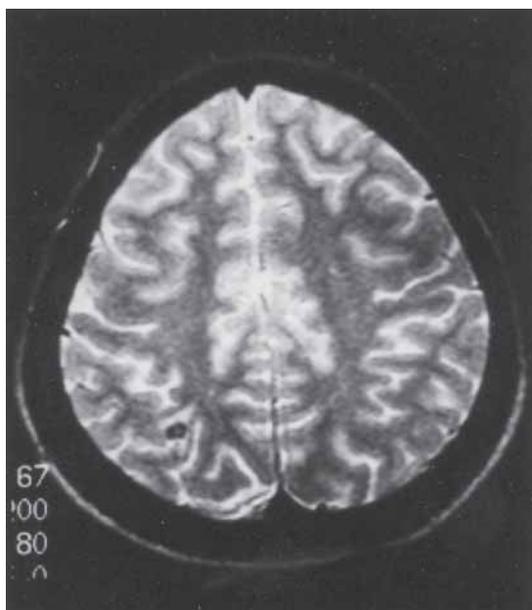


Figure 3. T2 weighted MRI of brain showing small round hypointense signal, which was also hypointense on T1 weighted image not shown suggesting calcified neurocysticercosis.

to be responsible for poor drug control and recurrence after stopping anti-epileptic medication (Figure 4).¹⁵ Healing by calcification and perilesional gliosis has been found to be the poor prognostic factors for long-term seizure control.¹⁶ Troublesome and annoying minor ictal symptoms have been reported in patients who develop perilesional gliosis.¹⁷

Neuro-imaging is essential to the diagnosis of neurocysticercosis. Brain MRI is superior for showing intraventricular or subarachnoid cyst, and for showing inflammation around a cyst whereas CT is better for showing the calcification of inactive lesions. However, recent MRI studies with gradient echo and reversed gradient echo-phase image have shown scolex visible within the so-called calcified lesion as visible on CT scan; these entrapped antigens have been shown to be responsible for intermittent immuno-allergic response, peri-lesional edema and seizure recurrence (Figure 5).¹⁸ There may be single or multiple cysts in different pathological stage. Carpio has proposed a classification system that corresponds to the viability of the parasite: active, transitional and inactive. Both CT and MRI can show the presence of the eccentric mural nodule (the invaginated scolex), an appearance when

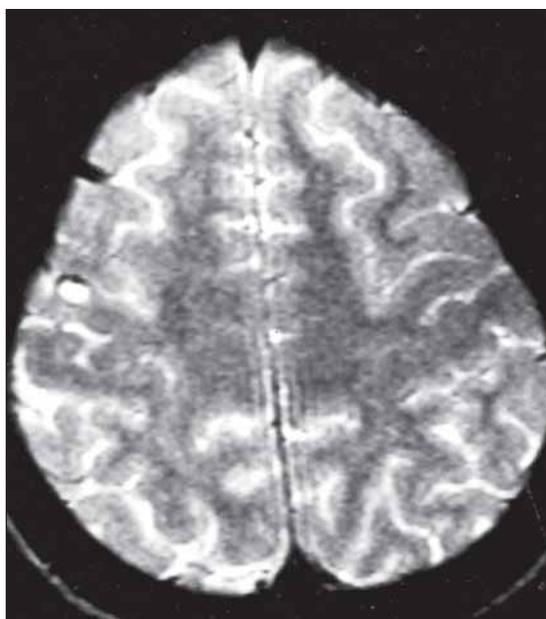


Figure 4(a)

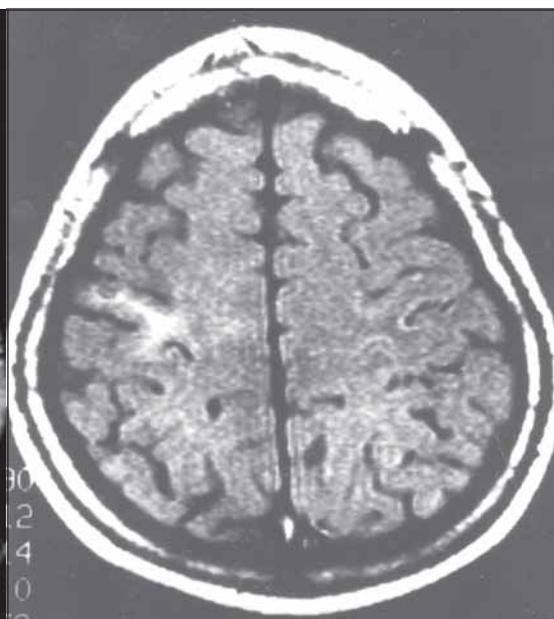


Figure 4(b)

T2 weighted (a) MRI of brain showing hypointense cystic lesion with hypointense signs suggesting degenerating neurocysticercosis with no peri focal hyperintensity to suggest perilesional edema. This lesion shows perilesional signal hyperintensity on magnetization transfer spin echo T1 sequence (b) suggestive of perilesional gliosis.

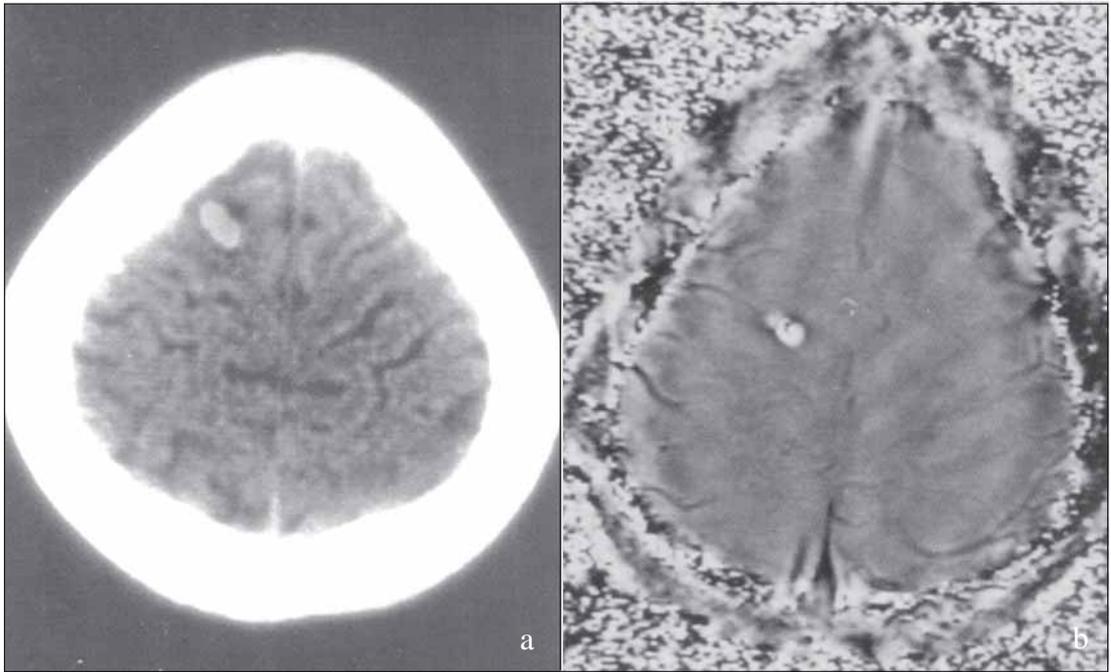


Figure 5 Calcified neurocysticercosis visible as hyper dense signal on CT Scan of brain (a) shows scolex (as hypointense signal within the hyperintense calcified cyst on corrected GRE image (b) on MRI of the same patient.

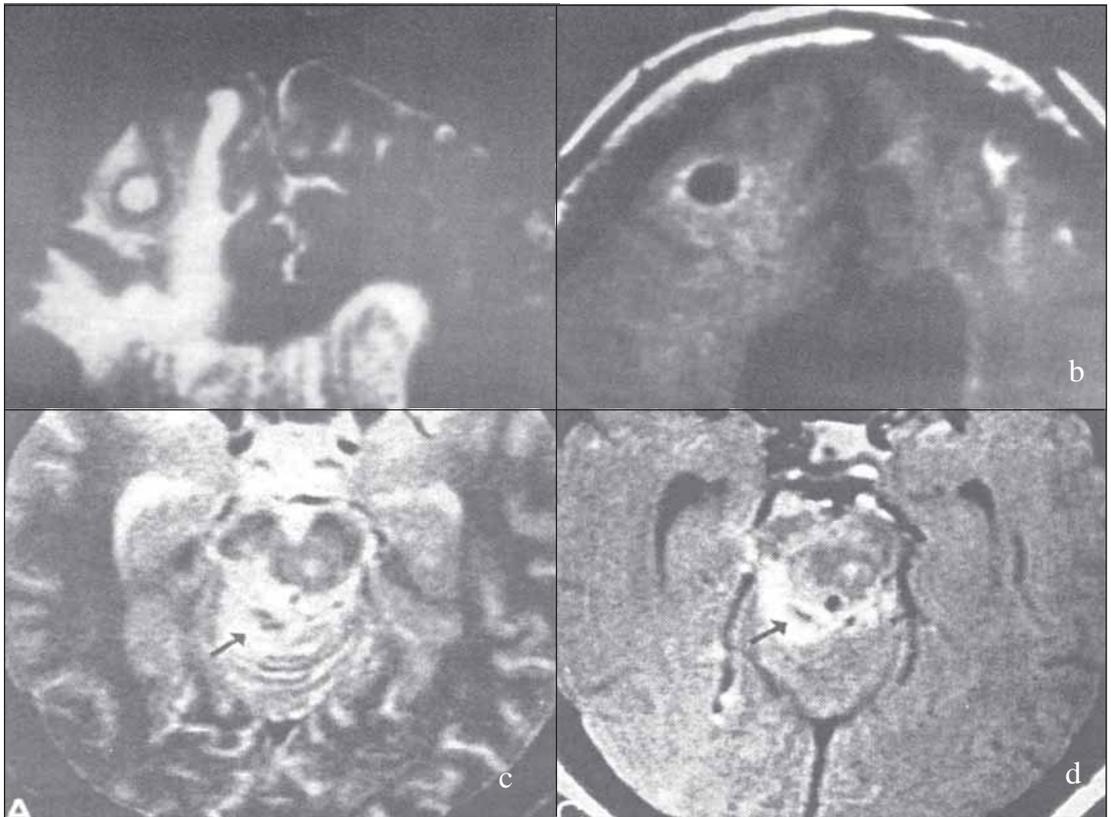


Figure 6. T2 (a and c) and T1 contrast (b and d) weighted images of brain showing T2 hyperintense and T1 hypointense cystic lesion with contrast enhancement (a and b) suggesting of cysticercosis and T2 hypointense (a and in c) and enhancing T1 hypointense (b and d) lesion suggesting of tuberculoma.

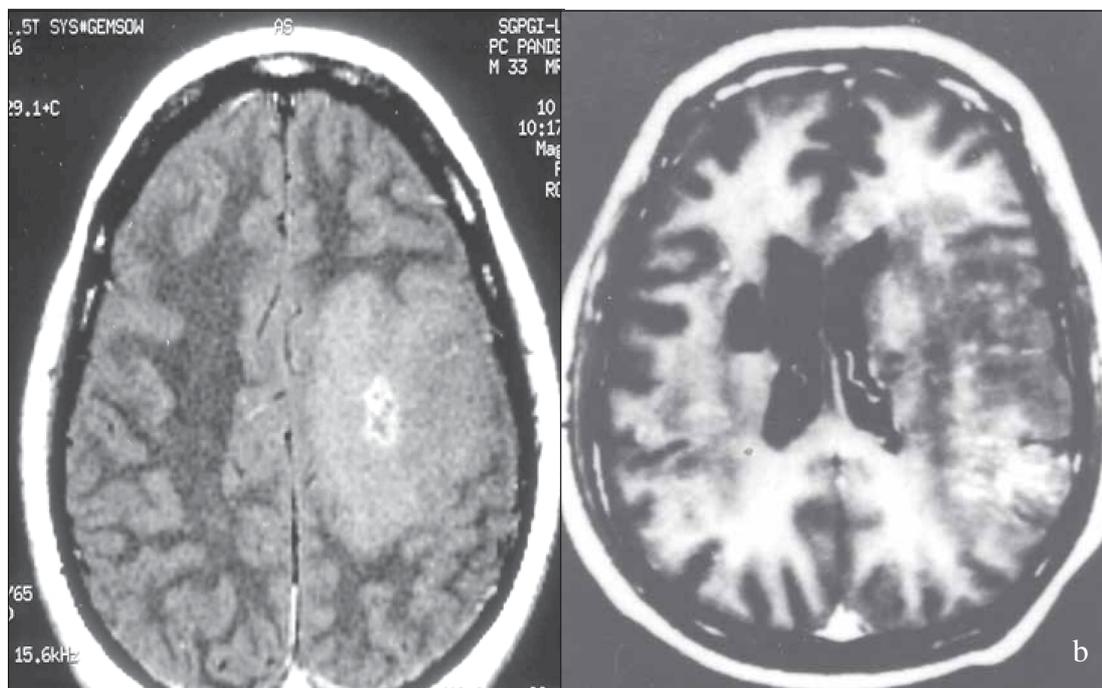


Figure 7. T1 contrast images of two patients of toxoplasmosis of brain showing conglomerating cystic appearance (a - localized form) and linear beaded appearance along Virchow Robin spaces (b - florid form).

multiple is pathognomonic of neurocysticercosis (starry night appearance). Distinction between two most common seizure producing granulomas, neurocysticercosis and tuberculoma, is difficult on CT scan or conventional MRI. However, magnetization transfer spin echo sequence of MRI (Figure 6)^{19,20} and calculation of magnetization transfer ratios¹⁹ have been shown to fairly distinguish these two lesions and different types of meningitis.

The treatment of neurocysticercosis with cysticidal drugs is controversial. The authors who advocate against the cysticidal drugs have several arguments in their favour: -(1) Sudden destruction of parasite may trigger an inflammatory reaction and more profound cicatrix formation that precipitates seizures²¹; (2) Single cysts are benign and manageable with anti-epileptic drugs alone and cysticidal drugs may be unnecessary²²; (3) Several cysts are adequately eliminated by host immune response²³; and (4) Elimination of parasite by cysticidal drugs does not in itself mean improvement in epilepsy control.²⁴ However, the recent studies have shown definite beneficial effect of cysticidal drugs at least in reducing the number of seizures with generalization. The number of cysts was also

reduced compared to controls in patients with multiple cystic lesions.²⁵⁻²⁷

Malaria

Malaria is the most common fatal parasitic disease. Overall approximately 2% of all patients with malaria have cerebral involvement and nearly 80% of patients who ultimately die have cerebral involvement. Cerebral malaria is fatal in 20% to 50% of affected patients. In a recent report from Nigeria where malaria is endemic, cerebral malaria is responsible for one third of seizures with fever in childhood.^{28,29}

Toxoplasmosis

Toxoplasma gondii is an obligate intracellular protozoan that infects numerous species of mammals and birds. The infection produces cysts containing trophozoites in various human tissues particularly in muscle and brain. Cerebral toxoplasmosis occurs in two clinical settings. During pregnancy it produces congenital toxoplasmosis in the fetus which is characterized by developmental delay, intracranial calcification, chorioretinitis and seizures. In immunocompromised patients, cerebral toxoplasmosis

produces nonspecific signs and symptoms of intracranial mass lesion and seizures. Porter and Sande described 115 patients with AIDS and cerebral toxoplasmosis. In the developing world however, toxoplasmosis may occur without HIV infection as well and linear beaded appearance on MRI may at times be diagnostic (Figure 7).³⁰ Frequent presenting findings were headache, confusion, and fever. Focal neurological deficits occurred in (69%) and seizure in (29%).³¹

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