The effects of antimicrobial and antiepileptic treatment on the outcome of epilepsy associated with central nervous system (CNS) infections

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SUMMARY
The course and outcome of epilepsy following central nervous system (CNS) infections has been poorly characterized. Likewise, the impact of antimicrobial treatment as well as other preventative and therapeutic interventions on the development of epilepsy following neurological infectious disorders has been insufficiently studied. The CNS infections that can cause epilepsy may be either acute or chronic-recurrent. For most acute infections, for example, viral encephalitis and bacterial meningitis, the effect of specific antimicrobial treatment on the development of epilepsy cannot be studied in a controlled manner due to logistic and ethical reasons. In the specific case of neurocysticercosis (NCC), the risk of seizures in the short term is reduced following either anthelminthic or corticosteroid treatment or both. The effect of anthelminthic treatment on seizure outcome in the long term has not been studied. Finally, treatment with antiepileptic drugs (AEDs) needs to be optimally defined in the case of epilepsy associated with neurological infectious disorders.

KEY WORDS: Central nervous system infections, Epilepsy, Seizures, Outcome, Antiepileptic drugs, Neurocysticercosis, Anthelminthic drugs.

A broad diversity of central nervous system (CNS) infectious disorders are noteworthy for their causal association with epilepsy, some of which have been reviewed elsewhere in this supplement issue (Garcia & Modi, 2008; Misra et al., 2008; Murthy & Prabhakar, 2008; Ngongou & Preux, 2008; Satishchandra & Sinha, 2008). Also reviewed in this issue are the course, outcome, and prognosis of epilepsy following various CNS infectious disorders. Herein, we discuss the effect of specific antinfecive treatment of the CNS infection and of long-term antiepileptic drug (AED) treatment on the course and outcome of the seizure disorder.

EFFECT OF ANTIINFECTIVE TREATMENT ON EPILEPSY

The treatment of CNS infectious disorders comprises of administration of specific antimicrobial and, in many cases, antiinflammatory agents. Ideally, treatment is intended not only to decrease mortality and morbidity during active infection but also to reduce the incidence of long-term complications and mortality thereof. The impact of antimicrobial treatment on immediate mortality and morbidity is unquestionable. The effect on long-term complications is however less certain. Examples of long-term complications of CNS infections include focal neurological deficits and sensorineural deafness following acute bacterial meningitis and cognitive and other neuropsychiatric sequelae and epilepsy following a variety of infections. An issue of concern is that by reducing mortality associated with more severe CNS infections, antimicrobial treatment might lead to an increase in long-term sequelae due to survival of more severe cases. The impact of specific and ancillary treatments of CNS infections on sequelae is an area of active study. The practice of administration of corticosteroids early in childhood and adult bacterial meningitis in order to prevent sensorineural deafness is a good example of the impact of therapeutic intervention on sequelae of meningitis (van de Beek et al., 2007). More recently, the administration of corticosteroids has also been shown to be associated with encouraging outcomes with regard
to late cognitive sequelae following bacterial meningitis (Ozen et al., 2006). The impact of corticosteroid administration on epilepsy or late unprovoked seizures has however not been studied because late seizures are uncommon and generally occur several months and even years after the meningitis episode, thus requiring larger samples and longer follow-up periods for their study.

The course of neurological infectious diseases may either be acute with rapid improvement following specific treatment (e.g., bacterial meningitis and viral encephalitis) or chronic, protracted or recurrent (e.g., neurocysticercosis [NCC] and slow virus infections). The effects of antiinfective treatment needs to be considered separately for acute and chronic infectious disorders. For many acute CNS infections, the occurrence of epilepsy is infrequent and often isolated and remote in the time scale so as to permit accurate estimation of its frequency. Furthermore, the effect of antiinfective treatment on subsequent epilepsy cannot be studied in a controlled manner because most anti-infective treatments constitute the standard of care, and hence denying such treatment is ethically unacceptable. In comparison, antiinfective treatments of certain chronic infectious disorders are in a state of evolution and still controversial, thus affording the opportunity of studying their effect on seizures and epilepsy in a controlled manner. For instance, several recent clinical trials have evaluated the effect of the anthelminthic drug, albendazole, and corticosteroids on seizures over short periods of time in NCC. The opinion generated from the results of several of these trials is summarized below.

Specific treatment of NCC and seizure outcome

A rational understanding of the effect of anthelminthic treatment in NCC requires appreciation of the heterogeneity of the presentation of the disorder (Garcia et al., 2002; Nash et al., 2006). For instance, NCC can localize to distinct anatomic compartments within the CNS including, most commonly, the brain parenchyma but also the subarachnoid spaces and ventricular system. Treatment options are in part determined by the location of NCC. In addition, the brain cysticercus goes through a series of evolutionary stages, which have bearing on treatment approaches as well (Garcia & Modi, 2008). The live or active cysticercus denotes the vesicular stage which is essentially a cystic parasite with an enclosed scolex without inflammation and edema in the surrounding brain parenchyma. Later, when the cysticercus undergoes degeneration, its clear cystic contents get replaced by opaque fluid and eventually by granulomatous material, representing the colloidal and granular-nodular stages of NCC. The brain parenchyma surrounding the degenerating cysticercus demonstrates inflammatory infiltrates, edema, neuronal loss, and astrocystic gliosis. Finally, the cysticercus involutes to a calcified-gliotic nodule with subsiding albeit often lingering inflammation in the surrounding brain tissue. All the stages of cysticercus are associated with seizures, though most typically, the latter occur during the degenerating, colloidal, and granulo-nodular stages. Theoretically, seizures in association with the degenerating stages are provoked and those that occur in the calcified-gliotic residual stage are unprovoked (hence, remote symptomatic seizures). However, it is increasingly being appreciated that the calcified-gliotic stage also harbors some parasitic residue, which may intermittently provoke inflammation and edema in the surrounding brain parenchyma and hence seizures. It is not known what proportion of seizures in relation to calcified-gliotic cysticercal residue is provoked by the inflammatory events, and conversely, what proportion is unprovoked (Nash et al., 2004). A careful longitudinal study, with serial imaging studies performed in close temporal relationship to seizures is required in order to determine the proportion of seizures in relation to calcified cysticerci that are provoked or not.

There is now consensus of opinion that anthelminthnic treatment significantly improves resolution of active (or live, vesicular), parenchymal cisticerci provided these are few in number (Nash et al., 2006). The beneficial effect of anthelminthnic treatment on seizure outcome in live vesicular cysticercosis is less certain. A recent double-blind randomized trial of albendazole in active parenchymal cysticercosis found a significantly reduced frequency of generalized seizures over a 30-month follow-up period with treatment (Garcia et al., 2004). Partial seizures were also reduced with treatment, but the difference between the treatment and placebo arms was not significant. The lack of significant decrease in all types of seizures and partial seizures in this trial could be due to the small sample size and few odd subjects in the treated arm having many seizures. The effect of anthelminthnic treatment on seizure outcome in the degenerating (colloidal/granulonodular) stages of parenchymal NCC has been studied in several small clinical trials. Degenerating cysticerci are visualized on imaging studies as enhancing lesions with surrounding edema (see Garcia & Modi, 2008, Fig. 2A–C). Four small clinical trials addressed the effect of albendazole on seizure outcome in 1–2 enhancing brain lesions due to parenchymal NCC (Padma et al., 1994; Baranwal et al., 1998; Gogia et al., 2003; Kalra et al., 2003). Despite heterogeneity in methods and samples, the trials found a reduction in number of seizures over 6- to 15-month follow-up periods. When data from the four trials were combined in a meta-analysis, it was found that 14% of treated subjects versus 32% of untreated subjects had seizures in the follow-up period, giving an odds ratio of 0.36 (95% CI: 0.21–0.62) (p < 0.001) (Del Brutto et al., 2006). Thus, there is some evidence that the anthelminthnic treatment is associated with improved seizure outcome over a short-term period in parenchymal NCC. The effect of treatment on seizure outcome over longer periods of follow-up has not been studied.
Apart from anthelminthic treatment, corticosteroid agents have been used in NCC for a variety of indications. Anthelminthic treatment often provokes seizures, focal neurological deficits and intracranial hypertension in parenchymal NCC by causing cyst degeneration and pericystic inflammation. The administration of corticosteroids concomitantly with albendazole is premised to reduce the incidence of adverse effects due to their anti-inflammatory actions. The idea that the corticosteroids alone could alter the clinical course and outcome in NCC perhaps developed out of anecdotal observations of symptomatic benefit with their use in NCC. Symptoms such as headaches and seizure exacerbations have been found to resolve with corticosteroid administration (Garg et al., 2004). In three clinical trials, the administration of either prednisolone (orally, 1 mg/kg/day for 10 days) or intravenous methyl prednisolone (one gram/day for 5 days) (in addition to standard AEDs) was associated with clinical and/or radiological benefits over 6–9 months (Mall et al., 2003; Garg et al., 2006; Prakash et al., 2006). There were some discrepancies in the outcomes of the trials, but these were mainly due to the small size of the individual trials, and when data from these trials were pooled, beneficial effects were quite apparent. In another two open-labeled trials, corticosteroids alone were compared to their coadministration with albendazole (Singhi et al., 2004; Sharma et al., 2007). The effects of the interventions on seizure outcome in these two trials were divergent, perhaps due to differences in methods.

The administration of anthelminthic treatment (albendazole) in live, vesicular parenchymal cysticercosis and of albendazole and corticosteroids independently in parenchymal enhancing cysticercus lesions is associated with improved radiological outcome. Whether the improved radiological resolution translates into better seizure outcome remains somewhat controversial. The effect of treatment on seizure outcome may vary according to the pathological stage of the cysticercus. Moreover, none of the trials so far have addressed seizure outcome over longer periods. Hence, longer-duration, large scale trials with sufficient power to dissect out the effect of treatment with albendazole and corticosteroids combined as well as independently on various evolutionary stages of parenchymal NCC are desirable.

**TREATMENT OF EPILEPSY**

The issues regarding long-term AED management are somewhat different for acute and chronic infections. For instance, in many chronic infectious disorders (e.g., CNS tuberculosis, human immunodeficiency virus [HIV] infection, and NCC), antimicrobial agents are required for long periods of time. Hence, interactions between antimicrobial (or anthelminthic or antiviral) agents and AEDs are of critical concern. These are considered elsewhere in this issue (Desai, 2008).

As with epilepsy in general, the need for, and duration of AED treatment of seizures occurring in the aftermath of neurological infections are determined by the natural history of seizures. Unfortunately, little information can be extracted from published medical literature regarding seizure outcomes and remission rates following CNS infections. Prospectively collected data on rates of seizure recurrence following a late unprovoked seizure due to bacterial meningitis or viral encephalitis and relapse rates following a period of seizure remission and withdrawal of AEDs are not available. In general, seizure prognosis in the aftermath of viral encephalitis or bacterial meningitis is likely to correspond to outcome in other remote symptomatic epilepsies. The average recurrence risk after a first unprovoked seizure due to any cause is estimated to be 51% (Berg & Shinnar, 1991). When the first unprovoked seizure is due to a remote symptomatic etiology, the pooled estimate for recurrence over 2 years is 57%. The average risk estimate of relapse of seizure(s) 1 year after AED withdrawal following a period of remission for all types of epilepsies is 25% at 1 year (Berg & Shinnar, 1994). Remote symptomatic epilepsy of any etiology increases this risk by 1.5 times.

No data are available regarding the proportion of individuals with postencephalitic (or postmeningitic) epilepsy that is eventually rendered refractory to medical treatment. Clinical characteristics and outcome following surgical treatment in highly selected populations of intractable epilepsy following viral encephalitis or bacterial meningitis from tertiary care clinics have however been described (Marks et al., 1992; O’Brien et al., 2002). As both encephalitis and meningitis produce diffuse brain damage, epilepsy following these antecedent illnesses is conjectured to be multifocal (Trinka et al., 2000a, 2000b). Accordingly, prognosis for cure following surgical treatment may not be good. However, a subset of intractable postencephalitic (or postmeningitic) epilepsy comprises of mesial temporal lobe epilepsy with unilateral hippocampal sclerosis (Fig. 1A–D). The prognosis for surgical cure in this subset has been shown to be excellent. In a series of individuals taken up for surgical treatment, it was shown that those with intractable epilepsy following meningitis mostly experienced the antecedent illness before 4 years of age and conversely, in postencephalitic epilepsy, the encephalitis episodes mostly occurred above the age of 4 years (O’Brien et al., 2002). Also, the postencephalitic group manifested with somatosensory and auditory auras more often indicating that the neocortical seizure onsets were more common in individuals with intractable epilepsy following viral encephalitis. It is not clear whether the propensity to neocortical localization in postencephalitic epilepsy is due to more diffuse brain damage in encephalitis in comparison to meningitis or an effect of age distribution on epileptogenic substrates. It may be premised that the hippocampus is relatively resistant to damage in older individuals. It follows that the insults required to produce neu-

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Figure 1.
(A–D) Serial MRIs in an individual with presumed Herpes simplex encephalitis showing (A) bilateral mesial temporal hyperintensities (more on the right side) on a coronal T2 weighted image during the acute encephalitic illness and follow-up FLAIR (B) and T2-weighted (C) images obtained 3 years later demonstrating right-sided hippocampal atrophy and sclerosis. Following the encephalitic episode, this individual developed medically-refractory complex partial seizures that were demonstrated to be of right anterior temporal origin on EEG telemetry (D). She remains seizure free after standard right anteromesial temporal lobe resection.

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Epileptic seizures following CNS infections are frequently considered to be due to a combination of several factors, including transient lesions and prolonged epileptogenic processes (Thompson & Remes, 2002). The clinical presentations vary from focal focal onset seizures of acute onset to occipital seizures following herpes encephalitis (Carpio & Hauser, 2002). The first-year risk of recurrence of seizures following a single seizure in NCC has been reported to be about 20%. This risk is likely to be an underestimate, because most patients with a first seizure due to NCC are initiated on AEDs, which would modify the natural history of seizures. A subset of parenchymal NCC comprises of the solitary cysticercus granuloma, for which the prognosis for seizure control appears to be excellent. These solitary granulomatous cysticerci frequently resolve with or without residual calcification. The average risk of a seizure relapse following discontinuation of AED treatment in resolved solitary cysticerci is about 14% (Gupta et al., 2002; Thussu et al., 2002; Rajshekhar & Jeyaseelan, 2004; Verma & Misra, 2006), which is substantially lower than the risk of relapse following AED...
discontinuation in unprovoked seizures. These data suggest AEDs may not be required for longer durations in solitary cysticercus granuloma and may be discontinued following radiological resolution.

**CONCLUSIONS**

Studies of antimicrobial treatment of both acute and chronic CNS infectious disorders need to address seizure outcome in the long term. In order to do so, they should be sufficiently powered as well as enduring. Future studies should closely incorporate imaging studies in order to understand the basis of epilepsy associated with neurological infectious disorders. The role of newer AEDs in the treatment of seizures and epilepsy associated with CNS infections needs to be evaluated; even so, characterization of the most cost-effective therapeutic strategy is required. Finally, an appraisal of the indications and approaches to surgical treatment of epilepsies following CNS infections needs to be undertaken.

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