What causes seizures in patients with calcified neurocysticercal lesions?

Neurocysticercosis (NCC), especially in the form of the single cysticercal granuloma (SCG), is one of the more common causes for new-onset seizures in endemic countries. Seizures in SCG usually occur during the active stage of the disease, as the parasite is degenerating. These lesions disappear in 80%-90% of patients within 3-6 months, with the majority of patients also becoming seizure-free.1,2 However, 15%-25% of patients continue to have seizures, necessitating treatment with antiepileptic drugs (AEDs), with some progressing to drug-resistant epilepsy.1,2

Approximately 10%-30% of SCGs heal by calcification, and these patients are at higher risk of developing epilepsy.1,2 In contrast to the well-recognized association between acute symptomatic seizures and SCGs, the association between epilepsy and calcified neurocysticercal lesions (CNLs) is rather controversial. CNLs are frequently encountered on CT scans of asymptomatic individuals, and studies from Latin American countries report that the majority are incidental lesions.3-6 These studies cast doubt on the epileptogenicity of CNLs.3-6 Conversely, there is circumstantial evidence that CNLs can cause epilepsy. In endemic countries, patients with epilepsy have a higher prevalence of calcified lesions than controls.4 Additional important evidence for the epileptogenicity of CNLs is the episodic appearance of edema surrounding the CNL after seizures.7

What is the mechanism by which CNLs cause epilepsy? One hypothesis is that episodic release of cysticercal antigens from the calcified lesions can lead to inflammation, perilesional edema, and seizures.8 However, this leaves unexplained the reason that CNLs are apparently asymptomatic in some patients. In a few of them, development of gliosis surrounding the CNL as a result of chronic inflammation can serve as a substrate for chronic epilepsy.2 In other patients, various host- or parasite-related or genetic mechanisms may contribute to epileptogenesis or its absence. This is corroborated by the differences in the nature and course of the disease between the Indian subcontinent and Latin American countries. Whereas SCG presenting as seizures is the predominant manifestation in the Indian subcontinent, multiple viable cysts with heavy parasite load is typical for Latin American patients, suggesting differences in underlying immune mechanisms.8

Identifying patients with CNLs who have a higher risk of recurrent seizures may help in planning the AED therapy. Determining whether CNLs are the cause of seizures in patients with drug-resistant epilepsy is of paramount importance during presurgical evaluation, especially if a CNL is associated with another potentially epileptogenic lesion, a situation not uncommon in endemic countries.

The study by Gupta et al.,9 published in this issue of Neurology, tries to answer some of the above questions. The authors studied 30 patients with single CNLs using dynamic contrast-enhanced MRI. Fifteen of these patients had seizures, and 15 were asymptomatic. Gupta et al. observed quantitative differences between symptomatic and asymptomatic groups in various perfusion indices. Median values of the rate transfer constant and leakage volume were higher in symptomatic patients than in asymptomatic patients, indicating a higher degree of blood-brain barrier (BBB) permeability in symptomatic individuals. They also observed higher serum levels of matrix metalloproteinase-9 (MMP-9) in symptomatic patients, which in turn were correlated with various perfusion indices. MMP-9 is a protease known to play a major role in the breakdown of the BBB in neuroinflammation; its serum levels increase in various neuroinfections. There were increased MMP-9 (R279Q) gene polymorphisms in subjects with seizures compared with those in asymptomatic and control subjects. Although a certain degree of BBB breakdown was found even in asymptomatic patients, the degree of BBB breakdown and inflammation was lower. These results indicate that symptomatic patients with CNLs have a greater degree of...
BBB breakdown, probably suggesting more profound levels of inflammation, which in turn may be related to MMP-9 gene polymorphism. Thus, the epileptogenicity in patients with CNL is related to degree of inflammation, which may be partly determined by genetic factors.

Apart from providing some explanation regarding the epileptogenicity of CNLs, these results have potential diagnostic and therapeutic implications. However, any result obtained from a small group of patients needs to be replicated and confirmed. The data have other limitations because they are based on MRI indices, which can only suggest that the amount of BBB disruption is higher in symptomatic CNLs. To provide a more robust answer, causative and temporal relationships with seizures need to be established. The majority of patients in the study had active seizures, but whether inflammation occurred in relation to seizures only or was also present during relatively long periods of seizure freedom needs to be determined. For such data to be useful in presurgical workups for epilepsy, there should be ways to distinguish between causative and incidental lesions. These preliminary results can form the basis of such future research.

Controversy remains regarding the best treatment approach in patients with SCG and acute symptomatic seizures. Although the majority of the present evidence suggests that anticyclicercal treatment with or without corticosteroids leads to relatively early disappearance of cysticercal lesions, the effects on long-term seizure outcome is uncertain. If the degree of inflammatory response at early stages is also proven to be the definitive factor for long-term seizure outcome, then reducing the level of inflammatory response, especially in genetically susceptible individuals, may result in better long-term seizure outcome. We await future studies for guidance in these important matters.

REFERENCES