Why Are There Seizures in Neurocysticercosis: Is It in the Genes?

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(See the article by Verma et al, on pages 1219–1225.)

“The demon slammed him to the ground and threw him into convulsions”


Neurocysticercosis is an ancient disease, yet it remains widely misunderstood [1]. Aristotle described the cystic form in the muscles of pigs, and similar descriptions were made by early Islamic scholars. In 1850, Kuchenmeister demonstrated the development of adult tapeworms in the intestines of prisoners who were fed Tae-nia solium cysticerci, and the fact that cysticercosis followed ingestion of T. solium eggs from tapeworms was also recognized at that time. English physicians carefully described all of the clinical manifestations of infection among British citizens returning home from India in the first half of the 20th century [2]. Neurocysticercosis was rarely diagnosed until the advent of noninvasive neuroimaging techniques of computed tomography and magnetic resonance imaging. Nevertheless, neurocysticercosis remains widely misunderstood in the medical community.

Many physicians assume that the presence of the parasites in the central nervous system (CNS) causes symptomatic neurocysticercosis. Indeed, biblical descriptions of seizure note invading demons (parasites?) seizing patients and throwing them to the ground. The pathogenesis is clearly more complex than simply having organisms in the brain. Neurocysticercosis is very pleomorphic [1, 3]. Cysticerci in the brain parenchyma go through a series of stages. The mature vesicular lesions develop within a few weeks, but they are typically asymptomatic and suppress the host inflammatory response. The lesions later become inflamed, with the host response gradually clearing the parasite. This transitional phase is frequently complicated by seizures. In some cases, the lesions will resolve completely. However, in other cases, resolution is incomplete, leaving a residual calcified lesion, which is often associated with chronic epilepsy [3]. Cysticerci in the brain parenchyma go through a series of stages. The mature vesicular lesions develop within a few weeks, but they are typically asymptomatic and suppress the host inflammatory response. The lesions later become inflamed, with the host response gradually clearing the parasite. This transitional phase is frequently complicated by seizures. In some cases, the lesions will resolve completely. However, in other cases, resolution is incomplete, leaving a residual calcified lesion, which is often associated with chronic epilepsy [3]. Cysticerci in the ventricles can be asymptomatic or cause symptomatic obstructive hydrocephalus with headaches, altered mental status, nausea, vomiting, and uncal herniation. Cysticerci in the subarachnoid space present with a range of clinical manifestations. Cysticerci located over the brain convexity resemble those in the brain parenchyma. When cysticerci develop in the fissures, they often enlarge dramatically. The cysticerci themselves or associated inflammation may lead to mass effect. Cysticerci in the basilar cisterns are often associated with basilar arachnoiditis and vasculitis, which may present with meningitis, communicating hydrocephalus, or stroke.

Several lines of evidence suggest a key role of host inflammation in the pathogenesis of neurocysticercosis. First, despite the fact that the cysticerci reach their mature size within a few weeks of infection, studies involving immigrants have demonstrated that there is typically a period of several years between exposure and development of symptoms [2, 4]. Autopsy series from areas of endemicity have demonstrated that there is typically a period of several years between exposure and development of symptoms [2, 4]. Autopsy series from areas of endemicity have demonstrated that symptomatic cysticerci are associated with CNS inflammation, whereas asymptomatic infections are typically not associated with inflammation [5]. Similar observations have been noted in some but not all neuroimaging studies. Finally, recent studies have noted that injection of associated granulomas induced seizures, and...
the seizures seemed to be mediated by host inflammatory molecules, such as substance P [6, 7].

In this issue of the Journal, Verma et al [8] report on CT studies involving patients with neurocysticercosis and their family members in villages in northern India where the disease is endemic. They note a surprising number of lesions in those individuals without symptoms. They also note an association of inflamed lesions with symptoms of seizures. However, no specific pattern on neuroimaging studies was associated with seizures in all cases. Verma et al [8] hypothesize that differences in host genetics might account for these differences. Because Toll-like receptors (TLRs), especially TLR4, play a key role in induction of the host inflammatory response, the authors tested subjects for polymorphisms in TLR4. They note that subjects with symptomatic neurocysticercosis were more likely to have polymorphisms TLR4 Asp299Gly and TLR4 Thr399Ile. These data demonstrate unequivocally an important role for host genetics in the pathogenesis of neurocysticercosis and show that this characteristic was strongly associated with the inflammatory response.

These results have important therapeutic implications for neurocysticercosis. First, too little attention has been given to the host response in studies of optimal treatment. For parenchymal disease, studies should clearly define the degree of inflammation noted on imaging studies [3]. Inflamed (ie, contrast-enhancing) lesions should be studied separately from nonenhancing lesions [9]. In the short term (ie, over a period of days to weeks), antiparasitic drugs can worsen the inflammatory response to the parasite and should always be accompanied by anti-inflammatory drugs, such as corticosteroids [10]. In the intermediate term (ie, over a period of weeks to months), antiparasitic drugs hasten resolution of lesions and decrease rates of recurrent seizures somewhat [9, 10]. However, better therapies are needed, and clinical trials should include studies to optimize anti-inflammatory drugs [3]. In the longer term (ie, over a period of years), current therapies do not seem to have an impact on the development of calcifications (which can break down, leading to inflammation and seizures) [3, 10]. Perhaps the host response should be more carefully addressed.

Similarly, more studies are needed on subarachnoid disease [3]. Although subarachnoid cysticercosis is less common than parenchymal disease, it accounts for a substantial portion of the morbidity and mortality from neurocysticercosis [11]. To date, there are no published controlled trials of treatment for subarachnoid cysticercosis. There is a consensus that therapies developed for parenchymal disease do not work well in subarachnoid cases. Alternative approaches have included higher doses of albendazole, prolonged or repeated courses of antiparasitic drugs, prolonged treatment with corticosteroids, use of methotrexate as a steroid-sparing agent, and even debulking endoscopic surgery. With aggressive treatment, some centers note very low associated mortality rates. However, available reports are confusing to those who are not experts in the field, with the result that there is marked variability in management and likely significant preventable morbidity and mortality. For example, we recently noted no fatalities among over 100 cases [12], whereas deaths continue to be recorded in national databases [13]. In summary, this study provides important insights into the role of host genetics and inflammatory responses in neurocysticercosis. Clearly, additional genetic studies are needed. At the same time, the study reinforces the importance of the host inflammatory response in symptomatic infection. Antinflammatory drugs play a key role in the management of neurocysticercosis, and additional studies are needed to help optimize this therapy.

References