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Perspective Piece

A Personal Account Regarding the Origin and Evolution of Controversies in the Management of Neurocysticercosis

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Abstract. A panel of experts from the Infectious Disease Society of America and The American Society of Tropical Medicine and Hygiene recently published guidelines for management of neurocysticercosis, showing that clinical manifestations as well as the stage of involution and the anatomical location of parasites must be taken into account before the start of a rational therapy. Soon thereafter, isolated opinions attempted to discredit these guidelines, arguing insufficient or inadequate evidence and suggesting that they should not be followed worldwide. In view of these conflicting reports, it is appropriate to review the origin and evolution of the controversy on the medical treatment of neurocysticercosis.

In view of the recent publication about the current guidelines for the diagnosis and treatment of neurocysticercosis by a panel of experts from the Infectious Disease Society of America (IDSA) and The American Society of Tropical Medicine and Hygiene (ASTMH),[1,2] and the criticisms raised by an external group.[3] I think it is appropriate to review the historical controversy on the medical treatment of neurocysticercosis, of which I have been an eyewitness for more than 30 years.

I belong to two different ages in the treatment of neurocysticercosis. This probably gave me the advantage of having a front seat to observe the curious (to say the least) sequence of events that started soon after the introduction of cysticidal drugs and continued for the following decades. During my residency training in neurology in Mexico City, under the mentorship of Julio Sotelo, I had the opportunity to get involved in one of the very first trials of albendazole management for parenchymal brain cysticercosis.[4] This "new" drug emerged as an alternative to praziquantel, introduced only a few years before. However, the anecdotal introduction of praziquantel by a veterinarian and a neurosurgeon who treated a young boy with parenchymal ring-enhancing lesions created controversy on the real value of this drug.[5] Despite this, the use of praziquantel continued in Mexico and several other Latin American countries, including patients with virtually all forms of the disease, even calcifications, and the attending physicians claimed high percentages of "cure" with virtually no adverse events at all.[6–8] In the middle of the controversy created by the aforementioned publications, two events augmented the confusion on the use of cysticidal drugs. First, the increasing number of patients with neurocysticercosis was diagnosed in the Southwestern United States, which led some physicians to treat these patients. They started using cysticidals in patients with several forms of the disease, including patients with a single parenchymal brain-enhancing lesion (the most frequent form of the disease seen in the United States at that time) and compared the results with nontreated patients, finding rather similar outcomes.[9] The second event was a report from India, showing severe adverse effects of cysticidal drugs—that even led to death—when used in patients with massive brain infections.[10]

When the initial chaos seemed to calm down, mostly because more serious works showed the efficacy of cysticidals drugs for destroying parenchymal brain cysts in the vesicular stage,[11,12] it appeared a study showing no differences in the rates of parasite destruction across patients treated with cysticidal drugs and nontreated patients.[13] Interestingly, the same authors had demonstrated an extremely high efficacy of albendazole just a few years ago, in the same population of patients,[14] just to conclude—several years later—that cysticidals were indeed effective for this purpose.[15] The study showing no effect of cysticidals on the destruction of cysts,[13] unfortunately led hundreds of neurocysticercosis patients deprived from adequate treatment for a number of years.

By that time, it was also argued that destruction of the cysts did not mean "cure," mostly because the trials were designed to assess whether cysticidals improved the neuroimaging of patients but not the clinical course of the disease.[16] This seems to me one of the most evident misconceptions in this story. Although the direct effect of cysticidal drugs is to destroy the parasites, the expected clinical benefit in the evolution of the seizure disorder is indirect and likely measurable in the long term.

By the early 1990s, there was preliminary evidence showing that the use of cysticidal drugs resulted in fewer seizure relapses in the follow-up than in nontreated patients, although these initial data did not come from randomized or double-blind studies.[17,18] To the surprise of many, some authors also started to claim that neurocysticercosis does not cause epilepsy, questioning whether this condition may occur just by chance in neurocysticercosis patients living in endemic areas.[19] So, at that time, many of the physicians involved in the management of patients with neurocysticercosis did not know where to stand because the use of cysticidal drugs and the relationship between neurocysticercosis and epilepsy had been questioned.

With the start of the new millennium, a randomized, double-blind trial conducted in adults with living brain parenchymal cysts showed that cysticidal drugs not only improve the neuroimaging studies by destroying living parasites but also lead to a better control of generalized seizures in the follow-up.[20] The same has been more recently demonstrated in

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another randomized study, where the use of albendazole was associated with fewer generalized (but not focal) seizure relapses.[21] Other similar well-conducted trials have been performed in children, but the problem here is that they included patients with single enhancing lesions, which may disappear spontaneously, and the efficacy of cysticidals might be difficult to evaluate.[22,23] Meta-analysis of controlled trials confirmed the efficacy of cysticidal drugs in these settings.[24–26] In addition, a Bayesian network meta-analysis showed that combination therapy with albendazole and corticosteroids is the single regimen that significantly reduced the risk of seizure recurrence at the follow-up.[27] On the basis of this evidence, guidelines from the American Academy of Neurology also favored the use of cysticidal drugs together with corticosteroids to treat patients with parenchymal brain cysts.[28] A problem with these guidelines is the inclusion of trials managing patients with viable cysts together with those managing patients with enhancing lesions (dying cysts), which make the pooled analysis difficult to interpret.

Back to the beginning of this article, guidelines proposed by the panel of experts from the IDSA and the ASTMH described in detail the diagnosis and management of the different forms of neurocysticercosis and proposed guidelines based on current knowledge of this disease.[1,2] As correctly noticed in those guidelines, neurocysticercosis is pleomorphic, and its diagnosis and treatment should be adapted according to this pleomorphism, prioritizing clinical manifestations as well as the stage of involution and the anatomical location of parasites. The next chapter in the history was an attempt to discredit these recently published guidelines, arguing insufficient or inadequate evidence, and suggesting that they should not be followed worldwide.[3]

If we look carefully at the literature, most of the chaos regarding neurocysticercosis management has been created by misconceptions on the parameters needed to decide the optimal management of neurocysticercosis according to the particular form of the disease in a given patient. However, as evidence has been growing, it is clear that cysticidals are the best therapeutic option for patients with viable parenchymal and subarachnoid cysticerci.[1,2] Probably, the only positive aspect of this continuous controversy is that it motivated more and more studies that finally concluded on the value of cysticidal drugs, at the expenses of leaving many patients untreated by physicians who got confused with the published inconsistencies.

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