

## NEW CONCEPTS IN THE DIAGNOSIS AND MANAGEMENT OF NEUROCYSTICERCOSIS (*TAENIA SOLIUM*)

HECTOR H. GARCIA, OSCAR H. DEL BRUTTO, THEODORE E. NASH, A. CLINTON WHITE, JR.,  
VICTOR C. W. TSANG, AND ROBERT H. GILMAN

*Department of Microbiology, Universidad Peruana Cayetano Heredia, Lima, Peru; Cysticercosis Unit, Instituto Nacional de Ciencias Neurológicas, Lima, Peru; Department of International Health, Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland; Department of Neurologic Sciences, Hospital-Clinica Kennedy, Guayaquil, Ecuador; Laboratory of Parasitic Diseases, Gastrointestinal Parasites Section, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland; Infectious Diseases Section, Department of Medicine, Baylor College of Medicine and Ben Taub General Hospital, Houston, Texas; Immunology Branch, Division of Parasitic Diseases, National Center for Infectious Diseases, Centers for Disease Control, Atlanta, Georgia*

**Abstract.** Human neurocysticercosis, the infection of the nervous system by the larvae of *Taenia solium*, is a major cause of epileptic seizures and other neurologic morbidity worldwide. The diagnosis and treatment of neurocysticercosis have been considerably improved in recent years. This improvement includes identification and sequencing of specific antigens and development of new assays for laboratory diagnosis, recognition of the frequency and significance of edema around old, calcified cysts (associated to symptomatic episodes), results of a randomized blinded control treatment trial on treatment efficacy for intraparenchymal disease showing a clinical benefit of decreased seizures, and a much better assessment of the frequency and spectrum of cerebrovascular complications. These advances now permit a much better integration of clinical, serologic, and imaging data for diagnosis and therapeutic purposes.

### INTRODUCTION

Neurocysticercosis (NCC) caused *Taenia solium* is responsible for a significant proportion of late-onset seizures in developing countries.<sup>1</sup> It is now frequently identified in the United States and other industrialized countries because of increased immigration and improved diagnostic methods.<sup>1,2</sup> In the normal life cycle of *T. solium*, humans host the 2–4-meter adult tapeworm that lives in the upper small intestine. Infective eggs are released from gravid proglottids at the distal end of the worm, and expelled with the stools of the tapeworm carrier. Pigs ingest these eggs in the stools and acquire the larval infection (cysticercosis) elsewhere in their bodies.

Human cysticercosis occurs when a human host ingests infective eggs by fecal contamination and replaces the pig as intermediate host. Humans are the only host for the adult tapeworm and thus the only source of cysticercosis for pigs or other humans (Figure 1). Human cysticercosis occurs anywhere in the human body, but becomes symptomatic almost exclusively in the nervous system (NCC) or the eye.<sup>3</sup>

The diagnosis and treatment of NCC have been considerably improved in recent years. This report reviews the recent additions to the diagnosis and management of four major presentations of human NCC: intraparenchymal disease, extraparenchymal disease, cerebrovascular complications, and calcified lesions.

### DIAGNOSIS

**Clinical diagnosis.** The clinical findings caused by cysticercosis are dependent upon the number, location, size, and viability or stage of degeneration of cysts. Because there are frequently multiple cysts at various locations and stages, clinical symptoms can be particularly varied. Larval cysts in the brain parenchyma are more common than those that are found in the ventricles or subarachnoid spaces and the clinical manifestations and treatment of these differ. Seizures (particularly late onset seizures) are the most common, troublesome clinical manifestation of parenchyma cysticercosis and come about commonly by two basic mechanisms. Viable cysts

with little or no enhancement or edema are usually not associated with symptoms.<sup>2</sup> It is when cysts are recognized by the host that an inflammatory response ensues commonly resulting in clinical symptoms. A magnetic resonance imaging (MRI) examination shows enhancement surrounding the cyst and some degree of edema.<sup>4</sup> A second recently recognized cause is perilesional edema around calcified cysticercal granulomas.<sup>5,6</sup> Less frequently, seizures can also be due to infarcts usually caused by inflammation associated with subarachnoid cysts or less commonly to inflamed subarachnoid cysts that are in contact with the brain parenchyma.<sup>7</sup>

Both parenchyma<sup>8,9</sup> and more frequently subarachnoid cysts can also cause symptoms secondary to seemingly unhindered growth leading to extraordinarily large cysts that result in symptoms and signs related to mass effects.<sup>10</sup> The mass effects are especially prominent when the cysticerci are inflamed either from spontaneous degeneration or after drug treatment. Hydrocephalus, one of the common more serious manifestations of cysticercosis, can present suddenly or chronically.<sup>11,12</sup> Free-moving ventricular cysts can abruptly obstruct cerebrospinal fluid (CSF) flow and when this occurs in the fourth ventricle can cause drop attacks, episodic vomiting, or even death. Conversely, chronic inflammation and fibrosis can obstruct any of the ventricles or the basilar foramina, leading to localized or generalized hydrocephalus. Subarachnoid cysts can also grow abnormally as a membranous and/or cystic mass called racemose cysticercosis.<sup>13</sup> These continually grow and commonly result in basilar arachnoiditis<sup>14</sup> with inflammation and fibrosis in and around critical structures, causing meningeal inflammation, hydrocephalus due to CSF outflow obstruction,<sup>12</sup> or cerebrovascular complications.

Cerebrovascular disease is one of the most feared complications of NCC and represents an important cause of death and disability in patients with the subarachnoid form of the disease. Cysticercosis-related stroke is caused by inflammatory changes in the wall of intracranial arteries located in the vicinity of cysticerci, and it is most often a focal process characterized by thickening of the adventitia, fibrosis of the me-

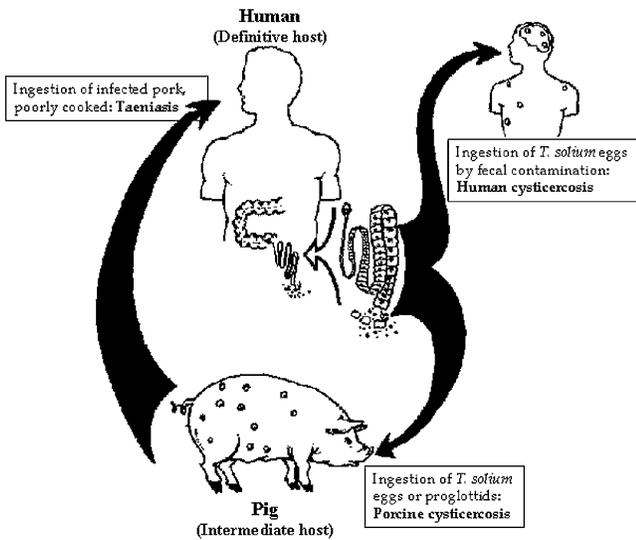


FIGURE 1. Life cycle of *Taenia solium* (from Garcia and Martinez<sup>54</sup> with permission).

dia, and endothelial hyperplasia, that may affect intracranial vessels of different sizes.<sup>15</sup> Stroke syndromes related to cysticercotic angiitis include 1) lacunar syndrome related to a small, deep, cerebral infarction located in either the internal capsule or the subcortical white matter; 2) large cerebral infarctions secondary to the occlusion of middle-sized intracranial vessels; 3) brainstem infarctions associated with the inflammatory occlusion of small branches of the basilar artery; and 4) hemorrhagic stroke related to the formation and subsequent rupture of a mycotic aneurysm located in the vicinity of subarachnoid cysticerci.<sup>7,16,17</sup>

Perilesional edema associated with calcified cysticerci is a newly recognized cause of seizures and/or other focal manifestations in chronically infected individuals. Previously, calcified cysticerci were believed to be clinically inactive and cause little or no disease. A number of recent studies implicate calcified cysticerci as a major cause of seizures in this population.<sup>5,6,18</sup> First, computed tomography (CT) and/or MRI studies of persons presenting with seizures in endemic populations commonly show typical calcifications as the only brain abnormality. Second, in a study of a randomly selected endemic population, calcifications were more frequently found in patients with a history of seizures compared with those without a history of seizures. Third, in some patients seizure foci have been localized to specific calcified cysticercal granulomas on electroencephalograms. And lastly, the most direct evidence is the presence of perilesional edema around calcified lesions usually associated with seizures or focal neurologic manifestations. Analysis of series of patients who have calcific cysticercosis and a history of seizures, suggests that the phenomenon is relatively frequent, occurring in approximately one-third to half of the patients. The natural course of this complication is unclear, but can at times be frequent and incapacitating. Because between 9% and 18% of unselected individuals in endemic areas have typical calcified lesions,<sup>19–21</sup> even a small increase in propensity to have seizures would affect large numbers of individuals.

**Serologic diagnosis.** Advances in serologic diagnosis include the identification and synthesis of specific antigens to

obtain consistent and highly sensitive assays in practical formats (easier to perform) that are not dependent on a continuous supply of parasite materials.

**Antibody assays for cysticercosis.** The Western blot for cysticercosis or the enzyme-linked immunoelectrodiffusion transfer blot (EITB), which uses lentil lectin purified glycoprotein (LLGP) antigens extracted from the metacestode of *T. solium*, has been the “gold standard” serodiagnostic assay since it was first described in 1989.<sup>22</sup> The diagnostic antigens, with molecular masses of 14, 18, and 21 kD, as well as some larger disulfide-bonded antigens, are all members of a family of closely related proteins known as the 8-kD antigens.<sup>23</sup> The genes for 18 unique, mature proteins have been identified. Nine of these proteins were chemically synthesized and tested in an enzyme-linked immunosorbent assay with a battery of defined serum samples, including 32 cysticercosis-positive serum samples reactive with the 8-kD antigens of LLGP on Western blotting, 34 serum samples from patients with other parasitic infections, and 15 human serum samples from healthy individuals. Several of these 8-kD antigens have high sensitivity and specificity and therefore are particularly suitable for use in serodiagnostic tests.

GP50, a *Taenia solium* protein diagnostic for cysticercosis has been cloned, sequenced, and characterized.<sup>24</sup> It is another diagnostic component of the LLGP antigens that has been used for antibody-based diagnosis of cysticercosis with the EITB assay for nearly 15 years. GP50 is a glycosylated and glycosyl-phosphatidylinositol-anchored membrane protein. The native protein has a molecular mass of 50 kD, but the predicted molecular mass of the mature protein is 28.9 kD. Antigenically active recombinant GP50 has been expressed in a baculovirus expression system. The antigenic activity of both the native and recombinant proteins is dependent upon the correct formation of disulfide bonds. GP50 purified from cysticerci has two homologs expressed in the adult worm: *T. solium* excretory/secretory (TSES)33 and TSES38 (see *Antibody assays for taeniasis*). Both are diagnostic for taeniasis. In spite of the amino acid similarities between GP50 and the TSES proteins, each appears to be a stage-specific antigen. A preliminary evaluation of recombinant GP50 (rGP50) in the EITB assay showed a specificity of 100% for cysticercosis and a sensitivity of 90% for cysticercosis-positive serum samples reactive with the GP50 component of LLGP.

A synthetic form of the 8-kD antigen (sTs18var1) and rGP50 protein was used in a quantitative Falcon assay screening test–enzyme-linked immunosorbent assay (FAST-ELISA) to measure the antibody responses in Peruvian pigs with cysticercosis. Three study designs were used. First, follow-up of the kinetics of antibody responses against these two diagnostic proteins in pigs with cysticercosis that were treated with oxfendazole. Second, measurement of the antibody response in experimentally naive-infected pigs. Third, follow-up of the maternal antibodies against rGP50 and sTs18var1 in piglets born from sows with cysticercosis. These studies showed that antibody responses against the two diagnostic proteins in the FAST-ELISA are quantitatively correlated with infection by viable cysts, with antibody activity to sTs18var1 being most responsive to the status of infection.<sup>25</sup>

**Antigen-detection assays for cysticercosis.** Detection of circulating parasite antigen reflects the presence of live parasites, establishes the presence of ongoing viable infection in the absence of definitive radiologic features, and may permit

quantitative verification of successful treatment.<sup>26,27</sup> From many assays reported, those based on monoclonal antibodies seem to achieve reasonable sensitivity and specificity when using CSF samples.<sup>27,28</sup> There is limited evidence on sensitivity or specificity when used with serum samples.<sup>29</sup>

**Antibody assays for taeniasis.** Humans can be infected with either the tapeworm and/or the larval form of *T. solium*, resulting in taeniasis or cysticercosis, respectively. The diagnosis and treatment of taeniasis is particularly important because this stage of the parasite produces large numbers of infective ova that after ingestion result in cysticercosis in humans and pigs. Treatment and elimination of tapeworms in carriers would eventually result in eradication of cysticercosis. A serologic taeniasis diagnostic test has been developed for laboratory use.<sup>30</sup> However, recombinant forms of the taeniasis diagnostic proteins are required to overcome the very limited supply of native protein and allow the development of a low-cost and field-applicable test with high sensitivity and specificity. Two-dimensional electrophoresis of TSES products from *in vitro* cultures of hamster-derived tapeworms identified five taeniasis-specific protein spots with molecular masses of 33 kD (pI 5.6, 5.3, 5.1) and 38 kD (pI 4.6, 4.5).<sup>31</sup> Protein sequencing and molecular cloning of these proteins showed that although endowed with different pIs, the proteins with the same molecular masses shared the same protein backbones known as TSES33 and TSES38. Their full-length cDNAs encode proteins with 267 and 278 amino acids, respectively. TSES33 and TSES38 were expressed in a baculovirus system. Both recombinant proteins were recognized by a panel of taeniasis, but not cysticercosis, patient serum samples, indicating that they can potentially replace the na-

tive proteins in the development of a taeniasis diagnostic test with a more efficacious format.

**Neuroimaging diagnosis.** Computed tomography and MRI provide objective evidence on the number and location of intracranial cysticerci, their viability, and the severity of the host inflammatory reaction against the parasites.<sup>4</sup> While these neuroimaging techniques have improved our diagnostic accuracy for NCC, some findings are nonspecific and the differential diagnosis with other infectious or neoplastic diseases of the central nervous system may be difficult. In such cases, proper integration of data provided by immunologic tests and epidemiologic data allow an accurate diagnosis in most cases.<sup>32</sup>

Neuroimaging findings in parenchymal NCC depend on the stage of development of the parasites.<sup>4</sup> Vesicular (living) cysticerci appear as cystic lesions within the brain parenchyma. The cyst wall is thin and isodense with the surrounding tissues and is generally not visible on imaging studies. The cyst fluid is hypodense and is clearly demarcated. These cysts lack perilesional edema, do not enhance after contrast medium administration, and characteristically show a bright nodule (hole-with-dot imaging) in their interior that represents the scolex (Figure 2). When parasites begin to degenerate (colloidal cysts), their appearance in CT and MRI examinations changes to ill-defined ring-enhancing lesions surrounded by edema (acute encephalitic phase). Perilesional edema is best noted by MRI using the fluid-attenuated inversion recovery (FLAIR) technique.<sup>4</sup> Granular cysticerci are degenerated parasites seen as nodular hyperdense lesions surrounded by edema or a rim of gliosis after contrast medium administration, and calcified (death) cysticerci appear on CT as small

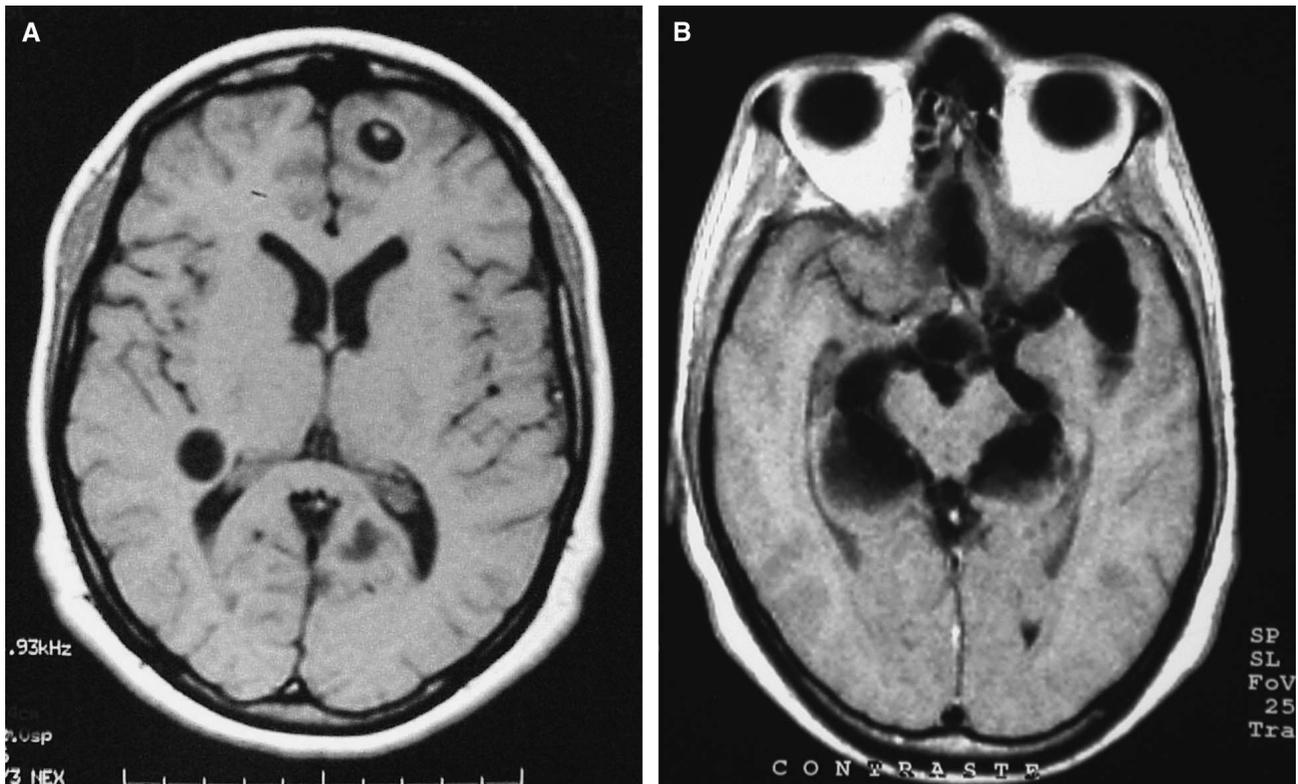


FIGURE 2. Magnetic resonance images (T1 sequence) showing parenchymal (A) and extra-parenchymal (basal cysticercosis) (B) viable neurocysticercosis.

hyperdense nodules without perilesional edema or abnormal enhancement after contrast administration; these lesions are usually not visualized by MRI. Conversely, when calcified are associated with perilesional edema and contrast enhancement, these are better seen by MRI (Figure 3).<sup>6</sup>

Cysticerci within the basilar cisterns can usually be identified by MRI, but the findings may be subtle and are usually not seen by CT. The most common CT finding in subarachnoid NCC is hydrocephalus. Most frequently, fibrous arachnoiditis is responsible for its development and is seen by CT or MRI as abnormal leptomeningeal enhancement at the base of the brain.<sup>33</sup> While most subarachnoid cysts over the convexity of the cerebral hemispheres are small, lesions located in the Sylvian fissure or within the basal CSF cisterns may reach 50 mm or more in size; these parasites usually have a multilobulated appearance, displace neighboring structures, and behave as mass occupying lesions.<sup>8</sup>

Cerebrovascular complications of subarachnoid NCC are well visualized by CT or MRI. However, the neuroimaging appearance of cysticercosis-related cerebral infarcts is the same as that of cerebral infarcts from other causes. The association of subarachnoid cystic lesions (particularly at the suprasellar cistern) and abnormal enhancement of basal leptomeninges, as well as CSF examination, usually suggest the correct diagnosis.<sup>7</sup> In such cases, angiographic studies or transcranial Doppler examination may show segmental narrowing or occlusion of major intracranial arteries (Figure 4).<sup>17,34</sup>

Ventricular cysts appear on CT images as cystic lesions. They are initially isodense with the CSF and are therefore not well visualized. However, their presence can be inferred from distortions of the ventricular system causing asymmetric or

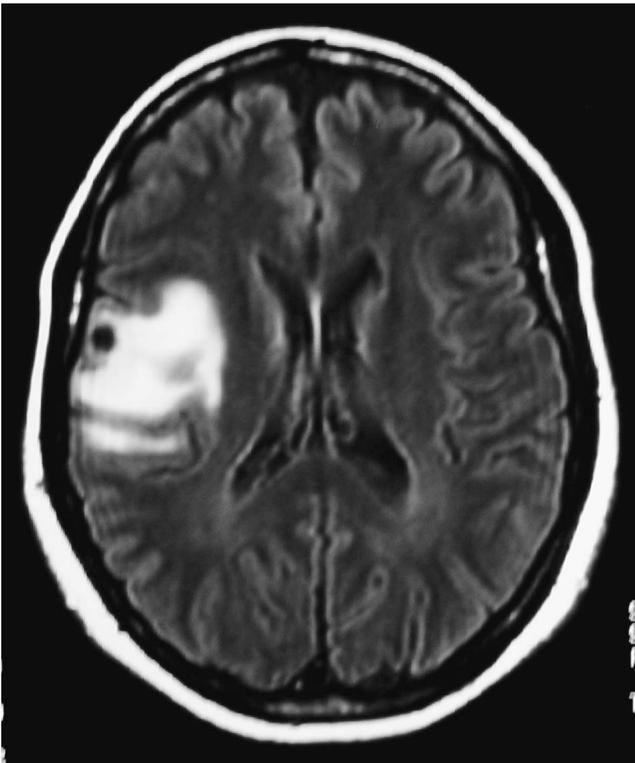


FIGURE 3. Magnetic resonance image (fluid-attenuated inversion recovery sequence) showing a calcified cyst with surrounding edema.



FIGURE 4. Vascular complications of neurocysticercosis. Digital angiography showing irregular stenosis of the left medial cerebral artery in a patient with subarachnoid cysticercosis involving the Sylvian fissure.

obstructive hydrocephalus. In contrast, most ventricular cysts are well visualized by MRI because their signal properties differ from those of the CSF, particularly using FLAIR techniques.<sup>35</sup> They may also move within the ventricular cavities in response to movements of the patient's head, (ventricular migration sign), a phenomenon that is better observed with MRI than with CT. Occasionally, this finding facilitates the diagnosis of ventricular cysticercosis.<sup>36</sup>

In patients with spinal NCC, CT may show symmetrical enlargement of the cord (intramedullary cysts) or pseudoreticular formations within the spinal canal (leptomeningeal cysts). On MRI, intramedullary cysticerci appear as ring-enhancing lesions that may have an eccentric hyperintense nodule representing the scolex.<sup>4</sup> Myelography still has a role in the diagnosis of patients with spinal leptomeningeal cysticercosis because it shows multiple filling defects in the column of contrast material corresponding to the cysts. Leptomeningeal cysts may be mobile (changing their position according to movements of the patient).

## TREATMENT

The treatment of NCC has been marked by an intense controversy on whether there are clinical benefits associated with the use of anti-parasitic drugs.<sup>37,38</sup> This controversy distracted clinicians from aspects of management that are more clear. First, all patients require adequate symptomatic therapy (e.g., anti-epileptic drugs and anti-inflammatory drugs). Second, management of intracranial hypertension when present is a crucial priority. Surgical therapy (e.g., CSF diversion) may be required. Third, some clinical presentations of NCC carry a higher risk for complications or death including most extraparenchymal forms (subarachnoid NCC, growing cysts, intraventricular NCC), cysticercotic encephalitis, etc. Fourth, treatment of NCC should be individualized based on cyst location, level or inflammation, and clinical presentation.

**Parenchymal NCC.** For intraparenchymal NCC with viable cysts, the current recommended regimen is albendazole

(ABZ) (15 mg/kg/day orally for seven days or longer).<sup>39</sup> This regimen is associated with destruction of most cysts, and a decrease in seizures of at least 45% (higher in seizures with generalization).<sup>40</sup> Albendazole is administered simultaneously with dexamethasone (0.1 mg/kg/day) for at least the first week of therapy. An alternative anti-parasitic drug, praziquantel (PZQ), can be used orally in a single-day regimen of three doses of 25 mg/kg given at two-hour intervals,<sup>41</sup> or the standard 15-day regimen of 50–100 mg/kg/day.<sup>42</sup> Efficacy of a single day course is good in patients with a single cyst or low cyst burdens, but it is less efficacious in those with heavier cyst burdens.<sup>43</sup> In general, PZQ has a slightly lower cysticidal efficacy than ABZ.<sup>42</sup> Also, steroids decrease serum levels of PZQ.<sup>44</sup>

Enhancing intraparenchymal lesions, corresponding to degenerating cysticerci, follow a favorable course whether or not treated with anti-parasitic drugs.<sup>45</sup> Either albendazole or a course of prednisone alone have been shown to enhance radiologic resolution and also seem to suggest an improvement in the prognosis of associated seizures.<sup>46,47</sup>

There is no reason to use anti-parasitic drugs to treat dead, calcified cysts. Also, there is no proven effective treatment of the episodic perilesional edema and contrast enhancement seen around calcified cysts at the time of relapse in symptoms. From uncontrolled observations and preliminary analysis of serial observations of an ongoing trial of corticosteroids in this newly described condition, steroids can only slightly shorten the duration of the edema (Nash TE, Garcia HH, unpublished data). There are no data about whether its use would affect the frequency of subsequent edema episodes.

**Subarachnoid cysticercosis.** There are no controlled trials on the management of subarachnoid NCC. In a series of patients treated with only CSF diversion, 50% died at a median follow-up of 8 years and 11 months.<sup>48</sup> Complications include mass effect, communicating hydrocephalus, vasculitis with strokes, and basilar meningitis.<sup>14,49</sup> More recently, case series using anti-parasitic drugs, corticosteroids, and shunting for hydrocephalus have been associated with an improved prognosis compared with older studies.<sup>10,33,50</sup> Thus, most experts consider subarachnoid NCC a clear indication for anti-parasitic therapy.<sup>39</sup>

The optimal dose and duration of anti-parasitic therapy for subarachnoid cysticercosis has not been established. In the largest cases series, Proano and others<sup>10</sup> treated 33 patients with giant cysticerci with ABZ (15 mg/kg/day for 4 weeks). There was only a single death (from aplastic anemia) at a median follow-up of 59 months. However, most patients required several courses of anti-parasitic therapy. Thus, a single course of albendazole for four weeks is likely inadequate. Similarly, the optimal dose and duration of anti-inflammatory therapy has not been well defined. One regimen that we have used begins with prednisone (60 mg/day for 10 days) and gradually tapering the dose by 5 mg/day every five days thereafter.

**Cerebrovascular complications.** Similarly, little is known about the management of cerebrovascular complications of NCC because there are no published trials on this subject. Current practice is to give corticosteroids to reduce the inflammatory reaction in the surrounding subarachnoid space.<sup>39</sup> Dexamethasone (16–24 mg/day) may be used during the acute phase of the disease, and oral prednisone (1 mg/kg/day) may be used for long-term therapy. Follow-up with re-

peated CSF examinations and with transcranial doppler may be of value to determine the length of corticosteroid therapy. The role of neuroprotective drugs in this setting is largely unknown.<sup>51</sup>

**Treatment of taeniasis.** Adequate treatment of tapeworm carriers is crucial to interrupt the transmission of cysticercosis. *Taenia solium* can be cured with a single dose of niclosamide (2 grams) or PZQ (5 mg/kg). Niclosamide is the drug of choice because it is not absorbed in the intestine, thus avoiding the risk of developing neurologic symptoms if the patient also has NCC. Treatment with either niclosamide or PZQ is supposedly more than 95% effective,<sup>52</sup> but no follow-up studies exist. Cestodes produce new proglottids from the neck region, immediately below the scolex. If the scolex is not expelled, it will regenerate to a full tapeworm in two months or less. Identification of the worm scolex expelled after treatment confirms cure, and can be significantly improved by using an osmotic purgative before and after anti-parasitic treatment.<sup>53</sup>

Received April 28, 2004. Accepted for publication April 28, 2004.

Financial support: This work was supported by research grants from the National Institutes of Health (Hector H. Garcia, Theodore E. Nash, Robert H. Gilman), The Wellcome Trust (Robert H. Gilman, Hector H. Garcia), the Food and Drug Administration (Hector H. Garcia, A. Clinton White), and the Bill and Melinda Gates Foundation (Hector H. Garcia, Victor C. W. Tsang, Robert H. Gilman). The American Committee on Clinical Tropical Medicine and Travelers' Health (ACCTMTH) assisted with publication expenses.

Disclosure: The sponsors had no role in the design or writing of this work.

Authors' addresses: Hector H. Garcia, Department of Microbiology, Universidad Peruana Cayetano Heredia, Lima, Peru, Cysticercosis Unit, Instituto de Ciencias Neurológicas, Jr. Ancash 1271, Barrios Altos, Lima 1, Peru, and Department of International Health, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD 21205, Telephone: 51-1-328-7360, Fax: 51-1-328-7382, E-mail: hgarcia@jhsph.edu. Oscar H. Del Brutto, Department of Neurologic Sciences, Hospital-Clinica Kennedy, Guayaquil, Ecuador. Theodore E. Nash, Laboratory of Parasitic Diseases, Gastrointestinal Parasites Section, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892-6612. A. Clinton White, Jr., Infectious Diseases Section, Department of Medicine, Baylor College of Medicine and Ben Taub General Hospital, Houston, TX 77030. Victor C. W. Tsang, Immunology Branch, Division of Parasitic Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA 30341. Robert H. Gilman, Department of International Health, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD 21205.

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