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# Proposed diagnostic criteria for neurocysticercosis

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# Abstract

Neurocysticercosis is the most common helminthic infection of the CNS but its diagnosis remains difficult. Clinical manifestations are nonspecific, most neuroimaging findings are not pathognomonic, and some serologic tests have low sensitivity and specificity. The authors provide diagnostic criteria for neurocysticercosis based on objective clinical, imaging, immunologic, and epidemiologic data. These include four categories of criteria stratified on the basis of their diagnostic strength, including the following: 1) absolute-histologic demonstration of the parasite from biopsy of a brain or spinal cord lesion, cystic lesions showing the scolex on CT or MRI, and direct visualization of subretinal parasites by funduscopic examination; 2) major—lesions highly suggestive of neurocysticercosis on neuroimaging studies, positive serum enzyme-linked immunoelectrotransfer blot for the detection of anticysticercal antibodies, resolution of intracranial cystic lesions after therapy with albendazole or praziquantel, and spontaneous resolution of small single enhancing lesions; 3) minor—lesions compatible with neurocysticercosis on neuroimaging studies, clinical manifestations suggestive of neurocysticercosis, positive CSF enzyme-linked immunosorbent assay for detection of anticysticercal antibodies or cysticercal antigens, and cysticercosis outside the CNS; and 4) epidemiologic-evidence of a household contact with Taenia solium infection, individuals coming from or living in an area where cysticercosis is endemic, and history of frequent travel to disease-endemic areas. Interpretation of these criteria permits two degrees of diagnostic certainty: 1) definitive diagnosis, in patients who have one

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absolute criterion or in those who have two major plus one minor and one epidemiologic criterion; and 2) probable diagnosis, in patients who have one major plus two minor criteria, in those who have one major plus one minor and one epidemiologic criterion, and in those who have three minor plus one epidemiologic criterion.

Cysticercosis, an infection caused by the encysted larval stage of the tapeworm *Taenia solium*, is one of the most common parasitic diseases of the nervous system in humans , and constitutes a major public health problem for most of the developing world.1-4 In addition, increased travel and immigration of people from endemic areas has caused a recent increase in the incidence of this parasitic disease in industrialized countries such as the United States, where hundreds of cases have been reported in past years.5-8 Conservative figures mention 50,000 deaths every year due to neurocysticercosis, and no less, than 20 million people infected by cysticerci.9 According to the International League Against Epilepsy, cysticercosis is probably the single most common cause of acquired epilepsy in the developing world, where prevalence rates of active epilepsy are twice those of developed countries.10 These numbers are the tip of the iceberg, as the actual prevalence of human cysticercosis is not known.

Neurocysticercosis is a common disease, but its diagnosis remains problematic. The most common clinical manifestations—seizures, headache, focal deficits—are caused by a broad range of neurologic conditions. Neuroimaging studies are usually abnormal but, in most cases, not pathognomonic.11 Serologic tests have been developed to support the diagnosis. However, older tests had low specificity and current assays have decreased sensitivity in patients with single lesions.12,13 In 1996, diagnostic criteria for cysticercosis, based on the objective evaluation of clinical, radiologic, immunologic, and epidemiologic data, were proposed (table 1).14 Whereas these criteria have proven useful in the diagnosis of this parasitic disease, concern has been raised about the specificity of some of them.15-17 After 4 years of experience, some of us have considered the chart too complex, as it was developed for the diagnosis of patients with neurocysticercosis as well as for those with exclusively muscular or cutaneous cysticercosis. With few exceptions, cysticercosis outside the nervous system rarely produces manifestations and it is not clinically relevant. Therefore, criteria devoted exclusively to the diagnosis of neurocysticercosis would be more practical yet more comprehensible than the original ones.

During a recent consensus meeting on cysticercosis held in August 2000 in Lima, Perú, a panel of experts agreed upon more accurate and stringent revised criteria for the diagnosis of neurocysticercosis. As in the original publication,14 the revised criteria include four categories—absolute, major, minor, and epidemiologic—stratified on the basis of their individual diagnostic strength (table 2). Absolute criteria allow unequivocal diagnosis of neurocysticercosis, major criteria strongly suggest the diagnosis but cannot be used alone to confirm the disease, minor criteria are frequent but nonspecific manifestations of the disease, and epidemiologic criteria refer to circumstantial evidence that favor the diagnosis of cysticercosis. Inasmuch as the new criteria are valid only for the diagnosis of neurocysticercosis, some have been adjusted according to its more specific scope.

In the original chart, interpretation of absolute, major, minor, and epidemiologic criteria resulted in three degrees of diagnostic certainty: definitive, probable, and possible (see table 1).14 However, we believe that the last category (possible diagnosis) does not have much diagnostic reliability, and we now include only two degrees of diagnostic certainty: definitive and probable (table 3). In addition, we agreed on more stringent criteria to consider a patient as having "definitive" neurocysticercosis in the absence of an absolute criterion (to avoid overdiagnosis). Previously, the presence of two major criteria were

# Absolute criteria

### 1) Histologic demonstration of the parasite from biopsy of a brain or spinal cord lesion

presence of at least one minor criterion plus exposure.

Visualization of the scolex with its suckers and hooks, or the presence of parasitic membranes in the histologi sections, identify the lesion as a cysticercus.18 However, biopsy of calcified cysticerci may not confirm the diagnosis, as the characteristic scolex or the membranes are no longer present.

### 2) Cystic lesions showing the scolex on CT or MRI

From the many neuroimaging findings of neurocysticercosis, only the presence of cystic lesions demonstrating the scolex should be considered pathognomonic.19 The scolex is visualized as a bright nodule within the cyst. This produces the so-called "hole-with-dot" imaging that is seen in some vesicular cysts located in the brain parenchyma, the subarachnoid space, or the ventricular system.20

### 3) Direct visualization of subretinal parasites by funduscopic examination

Because the retina is considered part of the CNS, patients with subretinal cysticerci may be considered to have neurocysticercosis. This does not apply to patients with cysticerci in the anterior chamber of the eye. Subretinal cysts are usually located over the macula and have a yellowish color with a central dark spot corresponding to the scolex. Subretinal cysticerci may rupture the retinal layers and enter the vitreous, a situation that permits the unique opportunity to visualize in vivo evagination and invagination movements of the parasite.21

# Major criteria

# 1) Lesions highly suggestive of neurocysticercosis on neuroimaging studies

In the original chart, all neuroimaging findings of neurocysticercosis (with the exception of cystic lesions with scolex) were included as a major criteria.14 However, we realize that some findings are more characteristic than others, and we have now classified them as "highly suggestive" and "compatible" lesions. Only highly suggestive lesions should be used as a major diagnostic criteria. These include: cystic lesions without a scolex, single or multiple ring or nodular enhancing lesions, and parenchymal round calcifications. Such CT and MRI findings may also be observed in other diseases of the CNS and must be interpreted with caution to avoid overdiagnosis of neurocysticercosis, particularly in HIV-infected patients or in those with evidence of a systemic disease.

Cysticerci-related cystic lesions may be found in the brain parenchyma, the subarachnoid space or the ventricular system.11,22 Parenchymal cysts are usually 5 to 20 mm in diameter and rounded. They tend to lodge in the cerebral cortex or the basal ganglia, and are less commonly found in the brainstem and cerebellum. The main differential diagnosis in these cases is with low-grade astrocytomas and cystic cerebral metastases. Subarachnoid cysts may attain a size of up to 60 mm, and usually have a multilobulated appearance. These lesions must be differentiated from congenital arachnoid cysts and epidermoid tumors. Intraventricular cysts may be located in any of the cerebral ventricles and may only become evident when they cause obstructive hydrocephalus. The presence of single or multiple ring or nodular enhancing lesions, although highly suggestive of neurocysticercosis, represents a diagnostic challenge. Many other conditions—tuberculomas, pyogenic brain abscesses, mycotic granulomas, and primary or metastatic brain tumors—may present with similar lesions on neuroimaging studies. Parenchymal cysticercal enhancing lesions are smaller than

20 mm in diameter, are most often located supratentorially, and rarely cause displacement of midline structures. Parenchymal brain calcifications are a common CT finding in neurocysticercosis. However, the specificity of this finding is not clear, because calcifications may be found in many other conditions including metabolic disorders, vascular malformations, intracranial neoplasms, congenital anomalies, and a variety of infections.23 Thus, only the presence of solid, dense, supratentorial calcifications, 1 to 10 mm in diameter, in the absence of other illnesses should be considered as highly suggestive of neurocysticercosis.

A common neuroimaging finding in neurocysticercosis is the presence of intracranial lesions in different evolutive stages—i.e., calcifications and cystic or ring-enhancing lesions.1 Inasmuch as the multiplicity of these findings provides further support for the diagnosis of neurocysticercosis, we are now considering the presence of two different highly suggestive lesions as two major diagnostic criteria.

# 2) Positive serum enzyme-linked immunoelectrotransfer blot (EITB) assay for the detection of antibodies to *T* solium glycoprotein antigens

Although many serologic assays for human cysticercosis have been reported, most of them are limited in value because of poor sensitivity and specificity. Only tests based on detection of antibodies specific for *T solium* antigens are reliable for clinical diagnosis and epidemiologic studies. To date, these are limited to those based on the use of purified glycoprotein antigens derived from T solium cysticerci. The current assay of choice is EITB using partially purified antigenic extracts.24 This assay has a documented specificity approaching 100% and a sensitivity of 94% to 98% for patients with two or more cystic or enhancing lesions.12,25 A major weakness of this test is frequent false negative results in patients with single intracranial cysticerci, in which fewer than 50% test positive.13 Sensitivity of specific antibody assays are als relatively low in patients with only calcified cysticerci.26 Because antibody assays reflect cysticercus infection in any tissue, not only patients with neurocysticercosis but also those with muscular or subcutaneous cysticercosis may test positive. Consequently, the results of even highly specific serologic tests must be evaluated critically because extraneural cysticercosis and even exposure without development of active infection may result in specific antibody development. Paradoxically, the sensitivity and specificity of antibody detection by EITB performed with CSF is lower than that performed using serum, even in patients with evidence of CNS involvement.27

The detection of antibodies to antigens of 26 kDa and 8 kDa by immunoblot using a crude antigenic preparation of *T solium* cysticerci has been shown to approach 100% specificity. 28,29 This assay has been less extensively assessed than that using purified *T solium* glycoproteins described previously, but has the potential advantage of the antigen preparation being simpler. The results need to be interpreted with more care, however, due to the presence of a number of nonspecific interactions with antigens with molecular weights close to those of the specific antigens. This assay is less sensitive than the glycoprotein based antigen EITB.30

#### 3) Spontaneously resolving small single enhancing lesions

Single enhancing lesions may occur in several infectious and neoplasic diseases of the CNS. However, Rajshekhar and Chandy31 demonstrated that when those lesions fulfill a rigid set of clinical and radiologic criteria, the diagnosis of neurocysticercosis can be established with a sensitivity of 99.5% and a specificity of 98.9%. Solitary cysticercus granulomas measure less than 20 mm in diameter, may be associated with edema not severe enough to displace the midline, and occur in patients with seizures, a normal neurologic examination, and no evidence of an active systemic disease. When those lesions resolve spontaneously, either

disappearing or transforming into a calcified nodule, the diagnosis of neurocysticercosis is almost certain. Solitary cysticercus granuloma account for 60% of neurocysticercosis cases reported from India,32 and have also been described in other regions of the world where this disease is endemic.33-35 Care should be taken not to interpret resolution of an intracranial lesion with the use of steroids as definitively indicative of neurocysticercosis because other diseases that may present with similar neuroimaging findings are known to respond to steroid therapy.

#### 4) Resolution of intracranial cystic lesions after therapy with albendazole or praziquantel

Several studies have shown that cysticidal drugs hasten the destruction of cysticerci,36-39 and the disappearance of intracranial cystic lesions or their transformation into calcified nodules after therapy with either albendazole or praziquantel should be considered a strong argument favoring the diagnosis of neurocysticercosis. Even for patients with enhancing lesions, some studies suggest the value of cysticidal drugs as a diagnostic tool as they accelerate the resolution of cysticerci-related enhancing lesions.40,41

# Minor criteria

#### 1) Lesions compatible with neurocysticercosis on neuroimaging studies

As previously noted, we consider that some neuroimaging findings in patients with neurocysticercosis do not have enough diagnostic strength to be considered major diagnostic criteria. These include CT or MRI showing hydrocephalus or abnormal enhancement of the leptomeninges, and myelograms showing multiple filling defects in the column of contrast medium. Hydrocephalus is common in patients with neurocysticercosis and may be related to the presence of ventricular cysts, ependymitis, or arachnoiditis causing occlusion of foramina of Luschka and Magendie.42 Ventricular cysts and ependymitis usually cause asymmetric internal hydrocephalus. Arachnoiditis causes enlargement of the lateral as well as the third and fourth ventricles, and is frequently associated with abnormal enhancement of the basal leptomeninges. Many other conditions-tuberculous and fungal meningitis, meningeal carcinomatosis-may course with similar findings. In these particular cases, CSF analysis may provide useful diagnostic clues that must be interpreted on the light of the clinical and radiologic manifestations of the patient.1 Finally, spinal subarachnoid cysts may appear as multiple filling defects in the column of contrast medium during a myelogram. This is also a nonspecific finding that may be observed in many other conditions affecting the spinal cord.

#### 2) Clinical manifestations suggestive of neurocysticercosis

Neurocysticercosis is a pleomorphic disease causing different clinical manifestations. Whereas definition of a distinct clinical picture of neurocysticercosis is not possible, large series have shown that seizures, focal neurologic deficits, increased intracranial pressure, and intellectual deterioration are the most common clinical manifestations of neurocysticercosis.5,43 More than 70% of symptomatic patients develop seizures, which in many of these cases are the primary or sole manifestation of the disease.44 Several studies have shown that neurocysticercosis is the single most common cause of adult-onset epilepsy in developing countries, and the presence of new onset seizures in an otherwise healthy middle-age individual coming from an endemic area is highly suggestive of neurocysticercosis.45-48 Other clinical manifestations of the disease include focal neurologic deficits, signs and symptoms of increased intracranial pressure, and intellectual deterioration.43 Fever is not a common manifestation of neurocysticercosis and its presence should suggest other diagnoses. As previously noted, diffuse cysticercotic arachnoiditis may induce similar changes in neuroimaging studies to those caused by tuberculous and fungal meningitis, conditions that usually cause fever.

# 3) Positive CSF enzyme-linked immunosorbent assay (ELISA) for detection of anticysticercal antibodies or cysticercal antigens

The detection of anticysticercal antibodies by serum ELISA has been used for the diagnosis of cysticercosis in endemic regions.49-52 However, recent studies have demonstrated a large number of false-positive and false-negative results.53 In contrast, the detection of anticysticercal antibodies by ELISA using CSF was 87% sensitive and 95% specific, and remains a useful tool for the diagnosis of neurocysticercosis in areas with limited access to the EITB assay.54 However, this test may be falsely negative in patients with parenchymal brain cysticercosis or in those with inactive disease, and it may be falsely positive in other helminthic infections.55

Some studies suggest that a specific antigen-detection ELISA using a monoclonal antibody is useful for the demonstration of excretory–secretory cysticercal antigens in CSF.56,57 The test has a sensitivity ranging from 72% to 86%, with false-negative cases restricted to patients with a single intracranial cysticercus. However, the specificity of this assay has not been adequately assessed on samples of patients with other diseases. Pending further experience with the use of this test, it should only be considered as a minor diagnostic criterion. Several other serodiagnostic tests have been proposed for immunodiagnosis of cysticercosis. These assays are not sufficiently well standarized at this time for inclusion as diagnostic criteria.

#### 4) Cysticercosis outside the CNS

From the pioneer studies of McArthur58 and Dixon and Lipscomb,59 it was considered that the presence of soft-tissue calcifications or palpable subcutaneous cysticerci in a patient with seizures strongly suggests the diagnosis of neurocysticercosis. This may be true, but in endemic regions a patient may have systemic cysticercosis and neurologic manifestations due to an unrelated cause. Therefore, a probable or even a definitive diagnosis of cysticercosis outside the CNS only provides circumstantial evidence favoring the diagnosis of neurocysticercosis. Definitive diagnosis of extraneural cysticercosis requires one of the following: 1) histologic demonstration of the parasite from biopsy of a subcutaneous nodule; 2) plain X-ray films showing multiple "cigar-shaped" calcifications in thigh and calf muscles; 3) direct visualization of a cysticercus in the anterior chamber of the eye; or 4) positive EITB test. Because the latter is already considered a major criterion for the diagnosis of neurocysticercosis, only the three previously enumerated findings should be included in this category of minor diagnostic criteria for neurocysticercosis.

# Epidemiologic criteria

Epidemiologic data, including the place of birth and residence and travel history, provide important information when evaluating patients with suspected neurocysticercosis. Cysticercosis is endemic in Latin America, sub-Saharan Africa, and in some regions of Asia, including the Indian subcontinent, China, Korea, and Indonesia. The disease is rare in most European countries, in North America, in Oceania, and in some Muslim countries of Asia and Africa.1 However, imported cases may occur even in these areas. Clinicians must be aware that neurocysticercosis is an infection acquired from a human tapeworm carrier and the disease is sometimes diagnosed in persons born in nonendemic countries who have never traveled to endemic regions.60-61 In such cases, it is of value to search for a close contact—usually a household contact—with a tapeworm infection. This finding will support the diagnosis of neurocysticercosis in a patient with suggestive clinical, radiologic, and immunologic criteria, and, by treating the tapeworm carrier, will permit the elimination of the source of contagion. A definitive diagnosis of *T solium* infection can only be established when the scolex or a gravid proglottid is available for microscopic examination.62 A

probable diagnosis can be suspected in those with history of having passed proglottids in feces as well as in those with positive stool examinations for *Taenia* eggs or with a positive coproantigen test.63 latter criteria should only be considered as probable indicators of *T* solium infection because they may represent an infection with *Taenia saginata*.

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# Table 1

Chart of diagnostic criteria and degrees of diagnostic certainty for human cysticercosis

Diagnostic criteria and degrees of certainty	Criteria
Absolute criteria	1. Histologic demonstration of the parasite
	2. Direct visualization of the parasite by funduscopic examination
	3. Evidence of cystic lesions showing the scolex on CT or MRI
Major criteria	<ol> <li>Evidence of lesions suggestive of neurocysticercosis on neuroimaging studies</li> </ol>
	2. Positive immunologic tests for the detection of anticysticercal antibodies
	<ol> <li>Plain X-ray films showing "cigar- shaped" calcifications in thigh and calf muscles</li> </ol>
Minor criteria	1. Presence of subcutaneous nodules (without histologic confirmation)
	2. Evidence of punctuate soft-tissue or intracranial calcifications on plain X-ray films
	3. Presence of clinical manifestations suggestive of neurocysticercosis
	<ol> <li>Disappearance of intracranial lesions after a trial with anticysticercal drugs</li> </ol>
Epidemiologic criteria	<ol> <li>Individuals coming from or living in an area where cysticercosis is endemic</li> </ol>
	2. History of frequent travel to cysticercosis-endemic areas
	3. Evidence of a household contact with <i>Taenia solium</i> infection
Degrees of certainty	
Definitive diagnosis	1. Presence of one absolute criterion
	2. Presence of two major criteria
	3. Presence of one major plus two minor and one epidemiologic criterion
Probable diagnosis	1. Presence of one major plus two minor criteria
	2. Presence of one major plus one minor and one epidemiologic criterion
	3. Presence of three minor plus one epidemiologic criterion
Possible diagnosis	1. Presence of one major criterion
	2. Presence of two minor criteria
	3. Presence of one minor plus one epidemiologic criterion

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Adapted from reference 14.

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#### Table 2

Revised diagnostic criteria for neurocysticercosis

Categories of criteria	Criteria
Absolute	1. Histologic demonstration of the parasite from biopsy of a brain or spinal cord lesion
	2. Cystic lesions showing the scolex on CT or MRI
	3. Direct visualization of subretinal parasites by funduscopic examination
Major	1. Lesions highly suggestive of neurocysticercosis on neuroimaging studies *
	2. Positive serum EITB <sup>†</sup> for the detection of anticysticercal antibodies
	<ol> <li>Resolution of intracranial cystic lesions after therapy with albendazole or praziquantel</li> </ol>
	<ol> <li>Spontaneous resolution of small single enhancing lesions<sup>‡</sup></li> </ol>
Minor	1. Lesions compatible with neurocystic ercosis on neuroimaging studies $\S$
	2. Clinical manifestations suggestive of neurocysticercosis <sup>//</sup>
	<ol> <li>Positive CSF ELISA for detection of anticysticercal antibodies or cysticercal antigens</li> </ol>
	4. Cysticercosis outside the $CNS^{n}$
Epidemiologic	1. Evidence of a household contact with Taenia solium infection
	2. Individuals coming from or living in an area where cysticercosis is endemic
	3. History of frequent travel to disease- endemic areas

CT or MRI showing cystic lesions without scolex, enhancing lesions, or typical parenchymal brain calcifications.

 $^{\dagger}$ Enzyme-linked immunoelectrotransfer blot assay using purified extracts of *Taenia solium* antigens, as developed by the Centers for Disease Control and Prevention (Atlanta, GA).

 $\frac{1}{2}$ Solitary ring-enhancing lesions measuring less than 20 mm in diameter in patients presenting with seizures, a normal neurologic examination, and no evidence of an active systemic disease.

 $^{\&}$ CT or MRI showing hydrocephalus or abnormal enhancement of the leptomeninges, and myelograms showing multiple filling defects in the column of contrast medium.

 $^{//}$ Seizures, focal neurologic signs, intracranial hypertension, and dementia.

<sup>¶</sup>Histologically confirmed subcutaneous or muscular cysticercosis, plain X-rav films showing "cigar-shaped" soft-tissue calcifications, or direct visualization of cysticerci in the anterior chamber of the eye.

ELISA = enzyme-linked immunosorbent assay.

#### Table 3

### Revised degrees of certainty for the diagnosis of neurocysticercosis

Diagnostic certainty	Criteria
Definitive	1. Presence of one absolute criterion
	2. Presence of two major plus one minor and one epidemiologic criterion
Probable	1. Presence of one major plus two minor criteria
	2. Presence of one major plus one minor and one epidemiologic criterion
	3. Presence of three minor plus one epidemiologic criterion

The presence of two different lesions highly suggestive of neurocysticercosis on neuroimaging studies should be considered as two major diagnostic criteria. However, positive results in two separate types of antibody detection tests should be interpreted only on the basis of the test falling in the highest category of diagnostic criteria.