Potential Pitfalls in the Diagnostic Criteria for Neurocysticercosis: Are Mimmicks Common?

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Abstract
This study reviews five cases of patients with secondary epilepsy who meet the diagnostic criteria for neurocysticercosis as well as compares 2001 and 2016 diagnostic criteria: in one case, a definitive diagnosis, and four probable diagnoses in the other four cases. All five patients are residents of regions where cysticercosis is endemic. Also, these patients showed clinical courses and neuroimaging studies highly suggestive of NCC, as well as positive ELISA testing for cysticerci in CSF (4 cases). We emphasize the importance of ruling out differential diagnosis especially in endemic areas and question the routine use of CSF ELISA testing for cysticerci antibodies as well as advice caution when interpreting cystic lesions as having a discernible scolex because potential mimics are not uncommon.

Keywords: Diagnostic criteria; Neurocysticercosis; Neuroimaging; T. solium

Introduction
Neurocysticercosis is a worldwide public health problem. It is the most important parasitic infection of the Central Nervous System (CNS) and one of the most common causes of secondary epilepsy in many endemic countries [1-8]. Also, epilepsy has a median lifetime prevalence of 15.8/1,000 in Latin American countries, and a median incidence of 138.2/100,000. Higher NCC estimates are associated with increased prevalence of epilepsy, pointing out to the need to improve our knowledge of the disease as a potential means to decrease epilepsy prevalence [9]. Although the flux of immigrants to developed countries has led to cases being reported in the United States and other first-world countries [8,10,11], its presentation in these locations is usually due to immigration from endemic countries instead of local transmission [7,8], and its prevalence is 0.2-0.6 per 100 000 inhabitants in some regions of the USA [8]. Diagnostic criteria by Del Brutto and cols have been published in 2001, and a set of revised diagnostic criteria have been released in 2016, aiming to simplify definitions and facilitate its applicability. Greater emphasis has been given to the need of neuroimaging. However, there are several pathologies that can present with similar or even indistinguishable characteristics. Here, we present a set of 5 cases of pathologies that mimicked NCC, described as potential differential diagnosis. All patients were inhabitants of an endemic region and presented with epilepsy.

Diagnosis
Neurocysticercosis is suspected from a patient’s clinical history. Its presentation usually varies from one patient to another, but the most frequent manifestation is seizures; focal signs, headache, and even secondary dementia due to intracranial hypertension are possible, regarding it as a great imitator, and can mimic almost any neurological disorder [7,8,12]. New diagnostic criteria have been published recently [13] emphasizing the importance of both clinical/exposure and neuroimaging criteria, aiming to increase diagnostic accuracy. Neuroimaging criteria, includes head CT, still the best screening procedure due to its lower cost and higher sensitivity for detection of calcified lesions, nevertheless brain MRI has a higher resolution, allows visualization of lesions in the posterior fossa without bony artifacts, and is better to evaluate intraventricular cysticercosis, brainstem cysts, and small cysts over the convexity of cerebral hemispheres [14]. The serologic analysis includes EITB (enzyme-linked immunotransfer blotting) with a sensitivity of 98% and higher specificity or detection of anticistercical antibodies in the CSF by ELISA (Enzyme-Linked Immunosorbsent Assay) and is 89% sensitive and 93% specific in patients with viable infections [8].

Classifications of the disease have been described according to imaging studies [15-17]. Recently, Del Brutto and collaborators [13] published diagnostic criteria for neurocysticercosis updating the previous 2001 diagnostic criteria. Main changes in the revised NCC diagnostic criteria include the division of neuroimaging and clinical/exposure criteria, requiring coexistence of both, as well as the distinction of the major and minor importance of each of them. Neuroimaging criteria have been rearranged as major, minor, and confirmative. Evidence of household contact with T. solium infection has been given greater importance, and epidemiological criteria have been included along with the clinical criteria. Absolute criteria have not changed, as shown in Table 1. According to the 2001 criteria [18] (current at the time that the patients presented to our hospital), the patients described in the following cases should have been diagnosed as definitive cases of neurocysticercosis. However, their clinical course and the lack of response to anticysticercosis treatment led all the way to a biopsy before establishing a true diagnosis. We used the 2016 diagnostic criteria (Table 1) [13], to reevaluate this cases to order to identify its potential usefulness and application, as well as to recognize potential pitfalls.

Case Description
Case 1
A 14-year-old boy presented with a one-month history of head...
aches. Three weeks later, generalized, tonic-clonic seizures; preceded by
two days of vomiting. The physical examination revealed papilledema.
A brain MRI was performed and showed cystic lesions without a dis-
cernible scolex, that enhanced with gadolinium, from 2 to 5 mm in di-
ameter, arbitrarily distributed throughout the cerebral parenchyma. The
lumbar puncture demonstrated an initial CSF pressure of 380 mmH20;
a differential cell count of 120 leucocytes, 60% segmented; glucose 24
mg/dL; and proteins 128 mg/dL. The ELISA testing for cysticercosis
was positive, and the equivalent of 1 acid-fast bacillus was found in CSF,
for which antimycobacterial treatment was initiated. The patient’s evo-
lution was monitored clinically and by analysis of CSF, which turned out
to be satisfactory. The MRI taken after one year of treatment was
normal.

Comment: Fifteen to twenty percent of tuberculosis is extrapul-
monary [19], but an estimated 10% of immunocompromised patients
develop tuberculosis in the CNS. The causal agent is Mycobacterium
tuberculosis. Tuberculous meningitis (MTb) is the most frequent
manifestation, lasting approximately two weeks in adults (1 day to 9
months). Patients show a normal thorax in 45% of cases when radi-
ological imaging is performed, a positive PPD skin test in 51% of cases,
and a mortality rate of 21% [20,21]. Hemiparesis, papilledema, and sei-
zures occur in 10 to 15% of patients. The diagnosis is suspected by the
patient's clinical history, microbiological studies, PCR studies in CSF,
as well as neuroimaging. The treatment for pharmaco-sensitive bacilli
consists of 2 months of isoniazid, rifampin, pyrazinamide, and strep-
tomycin, followed by 7 to 10 months of isoniazid and rifampin. The
treatment varied if resistance is noted. HIV testing is recommended in
patients with MTb [22] (Figure 1).

Case 2

A 12-year-old boy presented with a 6-month history of headaches,
vomiting, and generalized seizures. The general medical and neurologi-
cal examinations were normal. The simple and contrast-enhanced head
CT showed multiple hypodense (cystic) lesions with contrast-enhanced
annular forms, a finding that was confirmed in subsequent control im-
ageing (CT and MRI), with persistence of these same lesions, in spite of
treatment with albendazole for seven months and praziquantel for two
weeks. Analysis of the CSF demonstrated an aseptic liquid and positive
ELISA testing for cysticercosis. A biopsy was taken from one of the le-
sions, and North American blastomycesis was diagnosed. The patient
started treatment with amphotericin B and continued with fluconazole
as an out-patient. After four years of treatment with antymycotic agents,
the patient was asymptomatic.

Comment: Blastomycosis is a disease caused by a dimorphic fun-
gus, Blastomyces dermatitidis. Its most common presentation is sub-
acute or chronic pulmonary disease, while disseminated forms are
more frequent in the skin, bone, and the genital and urinary tract.
Blastomycosis in the CNS is quite rare. However, its presentation has
been reported in patients receiving treatment with ketoconazole for the
pulmonary form [23-25] (Figure 2).

Case 3

A 45-year-old man presented with a 6-year history of diabetes mel-
litus, a 2-year history of arterial hypertension, and nine years of pro-
gressive intense headaches. In October 1994 the patient presented a
simple-partial, left-hemifacial seizure with secondary generalization (1
minor criterion). Head CT showed a lesion highly suggestive of NC
(2 major criteria). Anticytostercosis treatment was initiated (inhabit-
ant of an endemic area for cysticercosis: 1 epidemiological criterion).
A left frontal craniectomy was performed due to a poor response to
pharmacologic treatment. The macroscopic lesion indicated NC, but the
microscopic analysis revealed histoplamosis. After surgery the patient
developed acute intracranial hypertension, aphasia, and right hemi-
paresis. The patient’s evolution turned out satisfactory after treatment
with fluconazole. At present he is asymptomatic.

Comment: The etiological agent of histoplamosis, Histoplasma
capsulatum, is a dimorphic fungus that causes systemic disease. It grows
in soil with a high nitrogen content, especially in areas contaminated
with the excreta of bats and birds, such as in chicken coops, attics,
barns, woodpiles, caves, and roosting areas such as parks. It is highly
endemic in the Ohio and Mississippi Valley regions of the United States,
the southern fringes of the provinces of Ontario and Quebec in Canada,
and scattered areas of Central and South America, as well as in south
and southeast Asia. This disease can remain latent in an individual for
many years after having abandoned an endemic area. Its principal man-

<table>
<thead>
<tr>
<th>Patient</th>
<th>Del Brutto NCC 2001 diagnostic criteria</th>
<th>Diagnostic certainty</th>
<th>Del Brutto NCC 2017 diagnostic criteria</th>
<th>Diagnostic certainty</th>
<th>Carpio 2016 NCC criteria</th>
<th>Diagnostic certainty</th>
</tr>
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<tbody>
<tr>
<td>Case 1</td>
<td>2 Major, 1 Minor, 1 Epidemiological</td>
<td>Definitive NCC</td>
<td>2 Major Neuroimaging, 2 Minor (1 Clinical/1 Exposure)</td>
<td>Definitive NCC</td>
<td>Multiple parenchymal vesicles without scolex associated with seizures, also positive ELISA</td>
<td>Definitive parenchymal NCC</td>
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<td>Case 2</td>
<td>2 Major, 1 Minor, 1 Epidemiological</td>
<td>Definitive NCC</td>
<td>2 Major Neuroimaging, 2 Minor (1 Clinical/1 Exposure)</td>
<td>Definitive NCC</td>
<td>Multiple parenchymal vesicles without scolex associated with seizures, also positive ELISA</td>
<td>Definitive parenchymal NCC</td>
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<tr>
<td>Case 3</td>
<td>1 Minor, 3 Major, 1 Epidemiological</td>
<td>Definitive NCC</td>
<td>3 Major Neuroimaging, 2 Minor (1 Clinical/1 Exposure)</td>
<td>Definitive NCC</td>
<td>Any combination of parenchymal cysticercus in different evolutive stages: degenerative nodular, and calcified granulomas</td>
<td>Definitive parenchymal NCC</td>
</tr>
<tr>
<td>Case 4</td>
<td>2 Major, 1 Minor, 1 Epidemiological</td>
<td>Definitive NCC</td>
<td>2 Major Neuroimaging, 2 Minor (1 Clinical/1 Exposure)</td>
<td>Definitive NCC</td>
<td>Any combination of parenchymal cysticercus in different evolutive stages: cystic lesion, and calcified granulomas</td>
<td>Definitive parenchymal NCC</td>
</tr>
<tr>
<td>Case 5</td>
<td>1 Absolute, 1 Major, 1 Minor, 1 Epidemiological</td>
<td>Definitive NCC</td>
<td>1 Absolute, 1 Major Neuroimaging, 2 Minor (1 Clinical/1 Exposure)</td>
<td>Definitive NCC</td>
<td>Single or multiple active parenchymal cysts, with at least one cyst with scolex</td>
<td>Definitive parenchymal NCC</td>
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Table 1: NCC criteria related to the patients presented [NCC criteria from Del Brutto and Carpio proposal related to the patients presented, all of them with the "Definite" criteria of neurocysticercosis].
manifestations are respiratory, and the disseminated form of the disease is rare except in immunosuppressed hosts. Ten to twenty percent of patients with disseminated disease present neurological manifestations, including meningitis, vasculitis, or even mass lesions [26-28].

Case 4

A 17-year-old boy presented with a 7-year history of partial seizures with motor signs in the upper right extremity and with secondary gen-
eralization (1 minor criterion). Neuroimaging showed a solitary granulomatous lesion in the left parasagittal, precentral region of the brain (1 major criterion). The CSF analysis demonstrated an elevated concentration of proteins, and the ELISA testing in CSF was positive for neurocysticercosis (1 minor criterion), for which anticysticerci treatment was begun (inhabitant of an endemic area for cysticercosis: 1 epidemiological criterion); however, it was not successful. Therefore, a biopsy was performed, and coccidioidomycosis was diagnosed. Treatment was immediately initiated with amphotericin B and later with fluconazole. At present the patient is receiving phenytoin and is asymptomatic.

Comment: The causal agent of coccidioidomycosis, Coccidioides immitis, is a dimorphic fungus endemic in semiarid climates and include such areas as the central San Joaquin Valley in California, Maricopa and Pima Counties in Arizona, and several western and southwestern counties in Texas. The disease is also endemic in the northern states of Mexico and parts of Venezuela, Paraguay, and Argentina. Cases have been reported in Central America as well. Its most frequent presentation is pulmonary, while isolated presentation in the CNS is quite uncommon. However, when it does occur, its usual manifestation is meningitis. The disseminated form of the disease only occurs in approximately 0.5% of cases, especially in immunocompromised individuals. There have been less than 40 cases of CNS infections of coccidioidomycosis that cause mass lesions reported in the medical literature [29-31].

Case 5

A 35-year-old female from a rural area without a history of comorbidities presented with a 1-month history of a dry cough, and three weeks prior presenting motor focal onset seizures without awareness impairment, initially one crisis per day, but with progression to Epilepsia partial continua in 2 weeks, requiring hospitalization. Head CT scan revealed two hypodense rounded lesions with contrast enhancement, highly suggestive of NCC, receiving treatment with albendazole and antiepileptics. Left hemiparesis was present after the episode of focal onset seizures but had been worse despite the absence of new crisis. Brain MRI was performed and revealed 2 extra-axial lesions with an isointense signal to brain parenchyma on T1, low signal and appearance of a scolex (isointense) on T2-FLAIR, a low signal on T2, without restriction on DWI, with notorious surrounding edema, and clear contrast enhancement. Despite the lack of a history for systemic symptoms, a body CT was performed revealing several hepatic, pulmonary, and one renal mass, a serum LDH of 1100, and HCG beta subunit of 1’505,752 leading to the diagnosis of choriocarcinoma.

Comment: It is essential to keep in mind that some pathologies might have rounded cystic lesions with pseudo scolex that might prompt us to consider a diagnosis of NCC. The characteristics of the two lesions in this patient are virtually indistinguishable from those of a vesicular colloidal phase of NCC. Remnants of neoplastic cells in metastasis, particularly (but not exclusive) in patients with single lesions should prompt the clinician to look for differential diagnosis [13]. Diffusion-weighted images (DWI) and fast imaging employing steady acquisition (FIESTA) can help to visualize these lesions [13], and magnetic resonance spectroscopy (MRS) can be of aid to distinguishing from other pathologies (neoplastic, with increase in choline, and infectious, as described in tuberculomas, with an inversion of the peaks of choline and creatine and a marked peak of lipids) [32] (Figures 3 and 4).
Discussion and Conclusion

NCC is a highly common entity, particularly in developing countries. Diagnostic criteria provide guidance, but knowledge about exceptions and precautions are essential when evaluating a patient with suspected NCC. These findings might apply to countries with a high number of cases of NCC, potentially biasing the evaluation and over-diagnosing the disease, or developed countries with few cases, raising the possibility to overlook the diagnosis of NCC. Neuroimaging techniques do not guarantee that the causal agent of these clinical manifestations is *Taenia solium*. It is not difficult to confuse other lesions with those caused by *T. Solium*, and many times these patients meet the diagnostic criteria for NCC previously mentioned and might lead to inappropriate treatment. It is only when anticysticerci treatment fails, and a biopsy is taken that the final diagnosis is reached. In the patients presented in this work, who often required a biopsy to reach a final diagnosis, it is noted that cystic-appearing lesions, that also enhance with contrast administration, are a somewhat common finding in several pathologies, particularly infectious, and that most often this patients might present with seizures, fulfilling 2 major neuroimaging and at least 1 clinical criteria for NCC, providing a "definitive" diagnostic certainty according to the revised diagnostic criteria for NCC (Table 2) [13], which might represent a potential pitfall for such criteria. In the fifth case, the presence of several cystic-appearing lesions, one of them with a dot, highly suggestive of a scolex, must also be carefully evaluated to prevent overlooking a metastatic lesion or other causes for pseudo-scolex, and neuroimaging techniques as DWI, perfusion, ADC, and MRS might be of great aid in this endeavor [17,33].

MRS of NCC lesions has shown elevated choline, lactate, succinate, alanine, lipid, and acetate, and decreased creatine and N-acetyl-aspar-

### Revised diagnostic criteria and degrees of diagnostic certainty for neurocysticercosis.

<table>
<thead>
<tr>
<th>Diagnostic criteria</th>
<th>Absolute criteria:</th>
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<tbody>
<tr>
<td>Histological demontration of the parasite from biopsy of a brain or spinal cord lesion.</td>
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<td>Visualization of subtretinalcysticercus.</td>
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<tr>
<td>Conclusive demonstration of a scolex within a cystic lesion on neuroimaging studies.</td>
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<tr>
<th>Neuroimaging criteria:</th>
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<td>Major neuroimaging criteria:</td>
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<tr>
<td>Cystic lesions without a discernible scolex.</td>
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<tr>
<td>Enhancing lesions.</td>
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<tr>
<td>Multilobulated cystic lesions in the subarachnoid space.</td>
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<td>Typical parenchymal brain calcifications.</td>
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<th>Confirmative neuroimaging criteria:</th>
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<tr>
<td>Resolution of cystic lesions after cysticidal drug therapy.</td>
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<td>Spontaneous resolution of single small enhancing lesions.</td>
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<td>Migration of ventricular cysts documented on sequential neuroimaging studies.</td>
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<th>Minor neuroimaging criteria:</th>
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<tr>
<td>Obstructive hydrocephalus (symmetric or asymmetric) or abnormal enhancement of basal leptomeninges.</td>
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<th>Clinical/exposure criteria:</th>
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<td>Major clinical/exposure:</td>
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<tr>
<td>Detection of specific anticysticercal antibodies or cysticercal antigens by well-standardized immunodiagnostic tests.</td>
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<tr>
<td>Cysticercosis outside the central nervous system.</td>
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<td>Evidence of a household contact with <em>T. solium</em> infection.</td>
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<th>Minor clinical/exposure:</th>
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<tr>
<td>Clinical manifestations suggestive of neurocysticercosis.</td>
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<tr>
<td>Individuals coming from or living in an area where cysticercosis is endemic.</td>
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<th>Degrees of diagnostic certainty</th>
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<td>Definitive diagnosis:</td>
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<tr>
<td>One absolute criterion.</td>
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<tr>
<td>Two major neuroimaging criteria plus any clinical/exposure criteria.</td>
</tr>
<tr>
<td>One major and one confirmative neuroimaging criteria plus any clinical/exposure criteria.</td>
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<tr>
<td>One major neuroimaging criteria plus two clinical/exposure criteria (including at least one major clinical/exposure criterion), together with the exclusion of other pathologies producing similar neuroimaging findings.</td>
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<th>Probable diagnosis:</th>
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<td>One major neuroimaging criteria plus any two clinical/exposure criteria.</td>
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<tr>
<td>One minor neuroimaging criteria plus at least one major clinical/exposure criteria.</td>
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Revised diagnostic criteria and degrees of diagnostic certainty for neurocysticercosis [13]. As such, caution must be taken when interpreting a positive ELISA testing in CSF (for IgM against T. solium) has a sensitivity of 95 to 98% [38,39], even though some authors mention a lower specificity [40], and lentil lectin purified glycoprotein enzyme-linked immune-transfer blot (ELITB) should be now used but also keeping in mind that its 100% specificity can drop as low as 50% would a single cysticercus be present [41]. Also, ELITB does not indicate CNS involvement, and antibodies can persist for long periods or even increase with exposure to the parasite in the absence of infection [41]. As such, caution must be taken when interpreting a positive result, always in the context of compatible clinical data.

Infectious diseases in neurology continue to be not only a diagnostic challenge but also a therapeutic one-one that requires a quicker and more effective approach. Recent revised diagnostic criteria for NCC underlies the importance of neuroimaging in the diagnosis of NCC. However, caution is advised when evaluating cystic lesions with contrast enhancement, and potential mimics of cystic lesions with an apparent scolex, because they most often are accompanied by clinical criteria, fulfilling definitive NCC according to the diagnostic criteria.

Further studies with an emphasis in differential diagnosis will be required to increase our diagnostic certainty when evaluating patients with suspected NCC but atypical clinical and neuroimaging manifestations.

Table 2: Revised diagnostic criteria and degrees of diagnostic certainty for neurocysticercosis [13].

References


