New Diagnostic Criteria for Neurocysticercosis: Reliability and Validity

Arturo Carpio, MD,1,2 Agnès Fleury, MD, PhD,3,4 Matthew L. Romo, PharmD, MPH,1,5 Ronaldo Abraham, MD,6 Jaime Fandiño, MD,7 Juan C. Durán, MD,8 Graciela Cárdenas, MD,3 Jorge Moncayo, MD,9 Cleonísio Leite Rodrigues, MD,10 Daniel San-Juan, MD,3 Marcos Serrano-Dueñas, MD,11 Oswaldo Takayanagi, MD,12 and Josemir W. Sander, MD, PhD, FRCP13,14

Objective: The diagnosis of neurocysticercosis (NCC) remains problematic because of the heterogeneity of its clinical, immunological, and imaging characteristics. Our aim was to develop and assess a new set of diagnostic criteria for NCC, which might allow for the accurate detection of, and differentiation between, parenchymal and extraparenchymal disease.

Methods: A group of Latin American NCC experts developed by consensus a new set of diagnostic criteria for NCC. A multicenter, retrospective study was then conducted to validate it. The reference standard for diagnosis of active NCC was the disappearance or reduction of cysts after anthelmintic treatment. In total, three pairs of independent neurologists blinded to the diagnosis evaluated 93 cases (with NCC) and 93 controls (without NCC) using the new diagnostic criteria. Mixed-effects logistic regression models were used to estimate sensitivity and specificity.

Results: Inter-rater reliability (kappa) of diagnosis among evaluators was 0.60. For diagnosis of NCC versus no NCC, the new criteria had a sensitivity of 93.2% and specificity of 81.4%. For parenchymal NCC, the new criteria had a sensitivity of 89.8% and specificity of 80.7% and for extraparenchymal NCC, the new criteria had a sensitivity of 65.9% and specificity of 94.9%.

Interpretation: These criteria have acceptable reliability and validity and could be a new tool for clinicians and researchers. An advantage of the new criteria is that they consider parasite location (ie, parenchymal or extraparenchymal), which is an important factor determining the clinical, immunological, and radiological presentation of the disease, and importantly, its treatment and prognosis.

Neurocysticercosis (NCC), the most common parasitic disease of the central nervous system (CNS), is still a cause of unacceptable morbidity and mortality in endemic areas.1,2 It is also an emerging public health problem in high-income countries.3–5 A current concern is that its prevalence remains unknown because there are...
problems inherent to its diagnosis. Diagnostic criteria for NCC were proposed in 2001. These have not yet been validated, but they have nevertheless made an important contribution to improving the knowledge of NCC. These proposed criteria, however, lack operational definitions and include a complex body of categories and degrees of certainty that can be difficult to apply in clinical practice. They may be useful in identifying individuals with parenchymal forms of NCC, but have limited use for people with extraparenchymal NCC. A broad consensus suggests that these criteria should be revised to incorporate current state-of-the-art scientific knowledge about NCC.

From the clinical, immunological, and pathophysiological points of view, parenchymal and extraparenchymal NCC are distinct entities, which cannot be covered by a single set of diagnostic criteria. To improve diagnosis of NCC, a panel of neurologists and neurosurgeons from Latin American countries endemic for NCC aimed to propose new diagnostic criteria for symptomatic NCC. The purpose of the exercise was to simplify the diagnostic criteria and clarify definitions currently used in the diagnosis, allowing them to be used by practicing physicians and adapted, as necessary, for epidemiological studies and clinical trials. While refining the diagnostic criteria to reflect improved understanding of the disease and new technologies, the panel retained all useful features of the existing diagnostic criteria.

The objective was first to establish a consensus among clinical experts on the most significant diagnostic criteria for NCC and then evaluate the reliability and validity of these new diagnostic criteria.

Materials and Methods

Phase 1. Developing Consensus Diagnostic Criteria

A panel of Latin American neurologists and neurosurgeons (R.A. [Brazil], J.C.D. [Bolivia], J.F. [Colombia], Ecuador [A.C.], and Mexico [A.F.]) was set up. Symposia were held from June 2011 to July 2013, including additional experts. One hundred fifty consecutive individuals with newly suspected NCC were pooled by the panel members from their own departments. On the basis of the discussions and analysis of epidemiological, clinical, immunological, and imaging findings of these 150 people, a proposal for a new set of criteria was drafted. The panel members further evaluated these criteria and incorporated modifications, until consensus was achieved on the new criteria (Table 1) and their operational definitions, to be further validated in the second phase of this study. The operational definitions were as follows:

**Parenchymal neurocysticercosis.** Parasites located in the parenchyma or in the subarachnoid space of the convexity or in the sulcus of the convexity. We grouped these three locations under the term “parenchymal” as their clinical (mainly seizures and headache), immunological (detection of antibodies and antigens is lower than in extraparenchymal forms), and cerebrospinal fluid (CSF) characteristics (CSF cells, proteins, and glucose concentration are frequently normal) are similar. Commonly used imaging tools (computed tomography [CT] and magnetic resonance imaging [MRI]) cannot differentiate them, particularly when parasites are located at the bottom of a sulcus.

**Extraparenchymal neurocysticercosis.** Parasites located in the basal cisterns of the subarachnoid space or in the ventricular system (intracranial hypertension is the main symptom). These two locations share clinical and immunological aspects (positive detection of antigens and antibodies) and their CSF (inflammatory) has the same anomalies.

**Cysticercus with pathological diagnosis.** The finding of parasites in brain biopsy, according to classical pathological descriptions.

**Neuroimaging definitions.** CT and MRI identify the four developmental phases of cysticerci (vesicular or viable phase, colloidal and granular-nodular in the degenerative phases, and calcified phase or dead parasite) when located in the parenchyma. Cysts in the vesicular phase appear as circumscribed, rounded, hypodense (or hypointense) areas, without enhancement by contrast media. In the MRI, the vesicular larva appears with a CSF-like intensity signal on all sequences, with no surrounding high signal on T2-weighted images. Both MRI and CT may show a high intensity or hyperdense, 2- to 3-mm mural nodule depicting the scolex, in the interior of some vesicular cysts. In the degenerative phases, contrast enhanced CT scan shows an annular (colloidal phase) or nodular (granular-nodular phase) enhancement surrounded by irregular perilesional edema. In these degenerative phases, the fluid content gives a slightly higher signal than CSF, sometimes isodense with the parenchyma on MRI-T1 and/or proton density-weighted images, and a high signal on T2 images. The capsule shows a higher signal than the adjacent brain, with thick ring enhancement on T1 images, whereas on T2 images there is a low ring signal surrounded by high signal, attributed mostly to edema. In the calcified phase, a nodule of homogenous high density on CT, or low intensity on proton-weighted MRI, is visualized. Parasites located in the subarachnoid space or inside the ventricular system emit an intensity signal similar to that of the CSF and commonly lack a visible scolex. Usually, there is no enhancement after the administration of intravenous contrast. Specific MRI sequences including diffusion-weighted MRI magnetization transfer ratio, three-dimensional (3D) constructive interference in steady state, fast imaging employing
steady-state acquisition sequences (FIESTA), and fluid-attenuated inversion recovery sequences have therefore been recommended for visualization of the cyst wall and, potentially, the scolex.\textsuperscript{17,18}

Positive immunological tests. The enzyme-linked immunosorbent assay (ELISA) and enzyme-linked immunoelectrotransfer blot (EITB) assay are used, either in sera or in CSF. EITB\textsuperscript{19} detects antibody whereas ELISA\textsuperscript{20} can be
used to detect either specific antibody or antigen. Regarding detection of antibodies, although the results differ between studies, their sensitivity seems to be higher in sera of people with parenchymal parasites, whereas in people with extraparenchymal ones, sensitivity and specificity are higher in CSF. Detection of antigens is mainly positive in cases of viable extraparenchymal cysts; its sensitivity is slightly higher in CSF than in sera.

**Seizures and epilepsy.** Definitions are based on the recommendation of the International League Against Epilepsy.

**Subcutaneous or muscle cysts location confirmed by biopsy.** Cysticerci in subcutaneous tissue have the appearance of spherical, smooth, mobile, and firm swellings, 1 to 2 cm in diameter, painless, and noninflammatory. Histological sections show the scolex with its suckers and hooks, or the presence of parasitic membranes.

“**Cigar shaped**” calcifications. Plain X-ray films show multiple oval, or cigar-shaped, muscular calcifications present throughout the upper and lower extremities, which corresponds to cysticerci located outside the CNS.

**Endemic countries.** Those countries in which the life cycle of the parasite can be reproduced, attributed to the presence of free-roaming pigs, absence of adequate disposition of human feces and of sanitary control, and scarcity of potable water.

**Hydrocephalus.** A disturbance of CSF formation, flow, or absorption, leading to an increase in the volume occupied by this fluid in the CNS.

**Inflammatory CSF.** Lymphocytic pleocytosis (between 15 and 300 cells per ml, 80–100% lymphocytes), mild elevation of protein (between 50 and 300 mg/dl), and hypoglycorrhachia (CSF glucose <40 mg/dl).

**Phase 2. Reliability and Validity of the Instrument.**

We evaluated the new diagnostic criteria in a multicenter, retrospective case-control study, adhering to the Standards for Reporting of Diagnostic Accuracy criteria. The study was initially approved by the ethical committee of the “Instituto Nacional de Neurología y Neurocirugía,” Mexico City, Mexico, and then local approval from each institution was obtained.

**REFERENCE STANDARD.** To differentiate between cases and controls, we used a reference standard. The only “gold standard” of NCC is the anatomopathological study, which is generally unavailable; the panel therefore considered that “response to cysticidal treatment” could be a reliable “reference standard.” All individuals with a cystic image (ie, viable parasites) included in this study therefore needed to receive cysticidal treatment and to have had post-treatment imaging studies (CT scan or MRI). Individuals in whom the post-treatment study showed evident changes in the cystic image (ie, disappearance or reduction of cysts) were considered to be cases, whereas those in whom no changes were observed were included as controls. Individuals with calcified (ie, inactive) parasites were also included as cases if pretreatment radiological studies detected a viable parasite that calcified after treatment. The cysticidal treatment used was albendazole 15 to 30 mg/kg/day for 10 days with corticosteroids (mostly prednisone 1 mg/kg/day). Pre- and post-treatment radiological studies were interpreted by experienced neuroradiologists, who evaluated the presence of changes in the images. Individuals with only calcifications were included as cases if pretreatment radiological studies detected a viable parasite that calcified after treatment. Individuals included as controls, because they fulfilled inclusion criteria for clinical manifestations or immunological testing (one or three of the inclusion criteria below) and had normal imaging, did not receive cysticidal treatment, because there was no reason to treat them.

Cases (individuals with confirmed NCC diagnosis) and controls (individuals with clinical, immunological, or imaging features compatible with NCC, but in whom NCC was excluded), were consecutively selected by review of medical charts of individuals seen in the previous 10 years. Some of them were included in clinical trials to evaluate efficacy of anthelmintic treatment in individuals with active NCC. No individuals included in this phase had been included in phase 1.

Individuals suitable for inclusion as cases or controls were initially selected according to the following inclusion and exclusion criteria:

**Inclusion criteria.** Individuals with at least one of the following criteria:

1. **Clinical manifestations:** people with focal seizures or generalized tonic-clonic seizures, or adults (≥16 years old) with intracranial hypertension or hydrocephalus.
2. **Imaging (CT or MRI):** any cyst (vesicular or colloidal) or granular-nodular or calcified lesion in parenchymal or extraparenchymal location.
3. **Immunological testing:** individuals with positive tests EITB or ELISA in serum or CSF.

A neuroimaging study was mandatory for those meeting criteria 1 or 3.

**Exclusion criteria.** Individuals in whom clinical, immunological, or imaging data were doubtful and could not be classified with certainty as cases or controls.

We organized three pairs of evaluators, blinded to all diagnoses, with the objective of determining reliability between pairs of evaluators and validity in two separate evaluations of the participants (Supplementary Table 1). The evaluators were neurologists from Brazil, Ecuador, and Mexico and were independent of the panel that developed the criteria. An anonymous database was set up containing the following information for cases and controls: clinical symptomatology; CSF characteristics (cell count and the percentages of lymphocytes, neutrophils and eosinophils, proteins, and glucose concentration); and results of immunological assays for antibodies and antigens. Pretreatment CT and MRI of all cases and controls were also collected. Each
of three pairs of the evaluators received a random sample of one third of the individuals (ie, cases and controls) included. The database of clinical information and images for these individuals was sent to the three pairs of evaluators, each with pair reviewing the same participants. Each evaluator in each pair reviewed the individual's images and clinical information and made diagnoses based on the newly proposed criteria and on the 2001 criteria. The same number of cases and controls of each of the participant countries was sent to each of the pair of evaluators.

Statistical Analysis
To compare the demographic and clinical characteristics of the cases and controls, we used the Mann–Whitney U test for the continuous variable (ie, age) and Pearson’s chi-square tests (or Fisher’s exact test, if appropriate) for all categorical variables. Cohen’s kappa coefficient was used to evaluate inter-rater reliability of the proposed criteria between each pair of evaluators, comparing diagnoses of NCC (including probable/definitive parenchymal and extraparenchymal disease) versus no NCC. An overall kappa was calculated by pooling the responses for the first evaluation of all participants (ie, the results of reviewers 1, 3, and 5 for all 186 participants) and comparing this with the pooled responses for the second evaluation of all participants (ie, the results of reviewers 2, 4, and 6 for all 186 participants).

To evaluate sensitivity and specificity, an estimated sample size of 93 cases and 93 controls per evaluation was included, assuming an expected sensitivity or specificity of 95% with a lower acceptable confidence interval (CI) of 85%, which was based on expert clinical opinion, because there were no previous studies setting a precedent. We used mixed-effects logistic regression models to determine sensitivity and specificity. We fitted one main model that included covariates for the new criteria, the 2001 criteria, and gold-standard diagnosis, with test diagnosis (ie, NCC vs no NCC) as the outcome. Random effects in the model were individual reviewer and study participant. For the new criteria, we fitted two additional mixed-effects logistic regression models, for parenchymal NCC and extraparenchymal NCC separately, with test diagnosis as the outcome (ie, parenchymal or extraparenchymal NCC vs no NCC) and gold-standard diagnosis as the predictor, with reviewer and study participant as random effects. When determining the sensitivity and specificity of the new criteria for parenchymal NCC, all cases with exclusively extraparenchymal NCC were excluded from the analysis, and, similarly, when determining sensitivity and specificity for extraparenchymal NCC, all cases with exclusively parenchymal NCC were excluded. This was done in an effort to only compare participants with either parenchymal or extraparenchymal NCC with participants without NCC (ie, controls). All analyses were done using SAS software (version 9.4; SAS Institute Inc., Cary, NC).

Results
Participants
We reviewed 250 consecutive individuals fulfilling the inclusion criteria, aiming to identify 93 cases and 93 controls. Once these numbers were reached, no further charts were reviewed. In total, 208 individuals were identified (Fig 1), but 22 were excluded because there was uncertainty associated with their diagnosis.

The 93 cases included originated from Ecuador (N = 26), Brazil (N = 29), and Mexico (N = 38). Parasite location was mainly parenchymal (N = 52; 55.9%), followed by extraparenchymal (N = 31; 33.3%) and in both locations (N = 10; 10.8%). In those with extraparenchymal NCC, parasites were in the subarachnoid space in 20 (48.8%) individuals, in the ventricular system in 18 (43.9%), and in both compartments in 3 (7.3%).

For controls, 93 neurological cases fulfilling the inclusion criteria were included from Mexico (N = 55), Ecuador (N = 25), Brazil (N = 10), and Bolivia (N = 3). Most of the 93 controls had a cystic lesion on imaging (N = 49; 52.7%), which were congenital subarachnoid cysts (N = 17; 34.7%), tumors (N = 14; 28.6%), encephalomalacia (N = 7; 14.3%), Virchow-Robin space (N = 6; 12.2%), and choroid plexus cysts (N = 5; 10.2%). The next most common inclusion criterion was seizures (N = 36; 38.7%), followed by hydrocephalus (N = 8; 8.6%).

Table 2 shows the main demographic and clinical characteristics of the cases and controls. There were no significant differences in age and sex between them. Intracranial hypertension was more frequent in cases compared to controls, and focal deficits were more frequent in controls compared to cases, whereas the other symptoms were similarly represented in the two groups.

Cytological and chemical analysis of CSF was available for 83 cases (89.2%) and 39 controls (41.9%).
ELISA in CSF was performed in 57 cases (61.3%) and 21 controls (22.6%). ELISA in CSF was positive in 43 cases (75.4%) and negative in all controls. In serum, ELISA was performed in 27 cases (29.0%) and in 3 controls (3.2%); 25 cases (92.6%) and 1 control (33.3%) were positive.

Reliability and Validity
Inter-rater reliability of the criteria for agreement between NCC and no NCC, as determined by Cohen’s kappa coefficient, ranged from 0.58 to 0.61, depending on review pair, and was 0.60 overall. Supplementary Table 2 summarizes the agreement between the two members of each of the three pairs of evaluators, each pair evaluating one third of the participants. Inter-rater reliability for the 2001 criteria was 0.57 overall (data not shown).

For the new criteria, sensitivity was 93.2% (95% CI: 86.8, 99.6) and specificity was 81.4% (95% CI: 67.1, 95.6; Table 3). For the 2001 criteria, sensitivity was 93.6% (95% CI: 87.6, 99.7) and specificity was 81.1% (95% CI: 66.7, 95.4). Differences between criteria in sensitivity and specificity were negligible and not significantly different (difference in sensitivity: 0.04%; difference in specificity: 0.03%; \( p = 0.85 \)). Sensitivity and specificity of the new criteria for parenchymal NCC were 89.8% (95% CI: 81.2, 94.7) and 80.7% (95% CI: 71.1, 87.6), respectively, and for extraparenchymal NCC, they were 65.9% (95% CI: 49.5, 79.3) and 94.9% (95% CI: 89.4, 97.7), respectively (Table 3).

Because the 2001 criteria do not make the distinction between parenchymal and extraparenchymal NCC, it was not possible to evaluate its validity for these subgroups. Among all pairs of evaluators, only 43.9% (18 of 41) of individuals with extraparenchymal parasites were diagnosed as having definitive NCC using the 2001 criteria.

Discussion
Since the publication of the first diagnostic criteria for NCC, new diagnostic tools have emerged and advances made in the understanding of NCC pathophysiology. It is now evident that parenchymal and extraparenchymal NCC are distinct entities with regard to diagnosis and treatment. Thus, we designed a practical and user-friendly diagnostic tool that maintains scientific rigor, but can also be used by the practicing physician in clinic and for research. We then evaluated reliability and validity.
validity of these new criteria. Overall, our results showed acceptable inter-rater reliability, based on a kappa of 0.60 (kappa of 0.61–0.80 = substantial strength of agreement; kappa of 0.41–0.60 = moderate strength of agreement; kappa of 0.00 = chance agreement).29 Next, we measured validity, which was also acceptable, with similar sensitivities and specificities for NCC overall and for parenchymal disease, but higher specificity and lower sensitivity for extraparenchymal disease.

An attribute of the new criteria is that it permits the distinction between parenchymal and extraparenchymal NCC. Using the new criteria, there was high sensitivity (89.8%) and specificity (80.7%) for detecting parenchymal disease and lower sensitivity (65.9%), but higher specificity (94.9%) for detecting extraparenchymal NCC. Reliability and validity were acceptable for clinical practice, but we would expect that routine use of 3D MRI sequences (eg, FIESTA) would improve sensitivity, particularly for extraparenchymal NCC.16–18,30 Further studies with these new MRI sequences, however, as well as a wider use of CSF analysis, are needed.31,32 Forty-one people had extraparenchymal parasites, of whom only 18 (43.9%) would have been diagnosed with definitive NCC using the 2001 criteria.8 In contrast, the new diagnostic criteria allowed an accurate diagnosis of definitive extraparenchymal NCC in the majority of them. A possible explanation for this improved ability to diagnose extraparenchymal NCC is that the new criteria have specific criteria (eg, hydrocephalus or positive CSF immunological test) compared with the very broad, nonspecific 2001 criteria8 (eg, clinical manifestation “suggestive” of NCC, positive immunological test for anticysticercal antibodies). Presence of antibodies in peripheral circulation may suggest previous systemic infections, but not necessarily active CNS infection.1,5 It has therefore been proposed that detection of antigens, which are very specific for viable infection, should also be included as an additional diagnostic criterion because its detection in CSF is specific to CNS infection.5,11

These findings are important given the different prognosis and treatment approach of parenchymal and extraparenchymal NCC. In general, parenchymal NCC has a good prognosis given that seizures, the main symptomatology, usually remit and refractory epilepsy rarely develops.13,33 In contrast, extraparenchymal NCC may cause permanent sequelae, such as cognitive problems and hydrocephalus, with a risk of death.10,25 Higher doses of cysticidal drugs and longer anti-inflammatory treatment are frequently required.34–36 In this context, the high specificity of these new criteria is of great relevance, demonstrating that the risk of false-positive diagnosis is low.

Strengths of this study include that it was multicenter and incorporated different Latin-American sites where NCC is endemic, with heterogeneity in the population assessed as they come from general hospitals and tertiary referral institutions. A practical reference standard was also developed and used. Our study also has limitations. Specifically, our specificity and its precision were lower than we anticipated estimating our sample size; there

| TABLE 3. Sensitivity and Specificity of New Diagnostic Criteria and 2001 Diagnostic Criteria |
|---------------------------------|---------------------------------|
|                                | New Diagnostic Criteria         | 2001 Diagnostic Criteria       |
| NCC overalla (N = 186)         |                                 |                                 |
| Sensitivity, % (95% CI)         | 93.2 (86.8, 99.6)               | 93.6 (87.6, 99.7)               |
| Specificity, % (95% CI)         | 81.4 (67.1, 95.6)               | 81.1 (66.7, 95.4)               |
| Parenchymal NCCb (N = 155)     |                                 |                                 |
| Sensitivity, % (95% CI)         | 89.8 (81.2, 94.7)               | NA                              |
| Specificity, % (95% CI)         | 80.7 (71.1, 87.6)               | NA                              |
| Extraparenchymal NCCc (N = 134) |                                 |                                 |
| Sensitivity, % (95% CI)         | 65.9 (49.5, 79.3)               | NA                              |
| Specificity, % (95% CI)         | 94.9 (89.4, 97.7)               | NA                              |

aNCC overall includes definitive/probable parenchymal NCC and definitive extraparenchymal NCC for the new criteria and any NCC diagnosis for the 2001 criteria.
bParticipants with only extraparenchymal NCC excluded. Parenchymal NCC is inclusive of probable and definitive categorizations.
cParticipants with only parenchymal NCC excluded.
NCC = neurocysticercosis; CI = confidence interval; NA = not applicable.
was, however, no precedent for this. Carrying out two evaluations of the same participants increased our statistical power and despite our results being useful, a larger sample size with different proportions of cases and controls should be used in future studies, based on our precedent. Future studies to evaluate these criteria should also be prospective to minimize potential selection bias. The cases and controls in this study had varying amounts of clinical information (eg, immunological tests or CSF analysis) available to the evaluators, which is perhaps a result of its retrospective design. This situation, however, reflects the information generally available in clinical practice in these settings. Other regions where NCC is endemic (eg, parts of Asia and Africa) were not included, where the clinical, immunological, and imaging characteristics of NCC may differ. To address this, it will be important to validate these diagnostic criteria in these regions in the future.

In conclusion, the new diagnostic criteria are reliable and valid not only for diagnosis of parenchymal NCC, but also for the diagnosis of extraparenchymal NCC and represent a valuable tool for clinical practice and research. The simplicity of the tool may provide an advantage for non-neurologist physicians in endemic countries to make an accurate diagnosis of NCC and ultimately to be used in primary health care. Further research is needed to improve evidence-based diagnostic techniques, such as imaging and molecular and immunological assays for NCC. With advances in technology, further modifications of our tool and revalidation will become necessary.

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Author Contributions
A.C., A.F., and M.L.R. conceived and designed the study. A.C., A.F., M.L.R., R.A., J.F., J.C.D., G.C., J.M., C.L.R., D.S.-J., M.S.-D., and O.T. were responsible for data acquisition and analysis. A.C., A.F., M.L.R., and J.W.S. interpreted the data and drafted the manuscript. All authors approved the final manuscript.

Potential Conflicts of Interest
Nothing to report.

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