Diagnostic criteria for neurocysticercosis: Some modifications are needed for Indian patients

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In India and other less developed countries the diagnosis of neurocysticercosis is frequently difficult because several other prevalent neurological disorders can present with a similar clinical and neuroimaging picture. Currently available international criteria seem to be helpful for the diagnosis of neurocysticercosis, however, these criteria have been criticized for not being effective in differentiating several other infective and neoplastic diseases of central nervous system (CNS), like CNS tuberculosis, from neurocysticercosis. In this article, modifications in the recent diagnostic criteria given by Del Brutto et al (2001) are being suggested, so, it can become more suitable for Indian patients. In India the overwhelming majority of patients with neurocysticercosis have either single enhancing or less frequently multiple enhancing CT lesions. Imaging and clinical features of various infective conditions, like tuberculosis, fungal granuloma, and parasitic granuloma, and of neoplastic conditions like cerebral metastasis, are remarkably similar. Keeping this in mind, the modification suggested in this article is to replace epidemiological criteria with the section diagnosis of neurocysticercosis with caution in certain situations. These situations are middle or old age, evidence of pre-existing tuberculosis or malignancy, pre-existing HIV infection and in patients with grossly abnormal neurological examination. In these situations, in the absence of one of the absolute criteria, it should be essential to consider and exclude all other likely possibilities before making a diagnosis of neurocysticercosis. However, because of the high prevalence of several disorders with similar features it is difficult to make reliable diagnostic criteria for neurocysticercosis, which are easy to use, and have a high specificity and sensitivity.

Key Words: Cysticercosis, CT, MRI, epilepsy, tuberculosis, seizures, Taenia solium

Neurocysticercosis is a common parasitic disease of the central nervous system (CNS). The precise incidence of neurocysticercosis in India is not known. Mahajan reported that 2.3 % of the general population in and around Chandigarh, had antibody titers positive for cysticercosis. Seropositivity was greater in rural areas and amongst the socioeconomically deprived persons with unhygienic habits. Chopra et al, in 1038 randomly selected patients of epilepsy, observed positive cysticercus haemagglutination test in approximately 26 % cases and 2 % healthy controls. An autopsy study conducted in a general hospital of another endemic country had reported a prevalence rate as high as 3.8 % in the general population. Neurocysticercosis is caused by the encysted larval stage, 'cysticercus cellulosae' of the pork tapeworm Taenia solium. The parenchymal cysts may remain dormant for many years, and symptoms (e.g. seizures) usually coincide with larval death and subsequent intense inflammatory reaction induced by larval antigens. Subsequently, the cyst transforms into a granuloma. The cyst then shrinks and granuloma eventually calcify or more frequently disappear completely. This clinicopathological pattern of spontaneous resolution or calcification has important implications for the correct diagnosis.
Table 1: Diagnostic criteria and degrees of diagnostic certainty for human cysticercosis

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute</td>
<td>1. Histological demonstration of parasite</td>
</tr>
<tr>
<td></td>
<td>2. Direct visualization of the parasite by fundoscopic examination</td>
</tr>
<tr>
<td></td>
<td>3. Evidence of cystic lesions showing scolex on CT/MRI</td>
</tr>
<tr>
<td>Major</td>
<td>1. Lesions suggestive of neurocysticercosis on neuroimaging studies</td>
</tr>
<tr>
<td></td>
<td>2. Positive immunological tests</td>
</tr>
<tr>
<td></td>
<td>3. Plain X-Ray films showing calcifications in thigh and calf muscles</td>
</tr>
<tr>
<td>Minor</td>
<td>1. Subcutaneous nodules</td>
</tr>
<tr>
<td></td>
<td>2. Soft tissue or intracranial calcification on plain X-rays</td>
</tr>
<tr>
<td></td>
<td>3. Clinical manifestations suggestive of neurocysticercosis</td>
</tr>
<tr>
<td></td>
<td>4. Disappearance of intracranial lesions after a trial with anticyclicercal drugs</td>
</tr>
<tr>
<td>Epidemiologic</td>
<td>1. Living or coming from endemic area of cysticercosis</td>
</tr>
<tr>
<td></td>
<td>2. Frequent travel to endemic areas</td>
</tr>
<tr>
<td></td>
<td>3. Household contact with Taenia solium infection</td>
</tr>
</tbody>
</table>

| Definitive: | 1) One absolute criterion; 2) two major criteria; 3) one major + two minor + one epidemiologic. |
| Probable:   | 1) One major + two minor; 2) one major + one minor + one epidemiologic; 3) three minor + one epidemiologic. |
| Possible:   | 1) One major; 2) two minor; 3) one minor + one epidemiologic. |

Why do we need Indian diagnostic criteria?

Unfortunately, the majority of Indian patients with neurocysticercosis can not satisfy several items even of the new diagnostic criteria. For example, direct visualization of subretinal parasite is rare in India. Non-enhancing cystic lesions on computed tomography (CT) or magnetic resonance (MR) imaging showing scolex constitute a small fraction of patients with neurocysticercosis. In India, the overwhelming majority of patients of neurocysticercosis have single enhancing lesions, multiple enhancing CT/MR lesions are also not uncommon. These single or multiple lesions pose a challenge both to radiologists and clinicians. Imaging and clinical features of tuberculoma are exceedingly similar to that of neurocysticercosis and it is difficult to differentiate between these two conditions. Because of their high prevalence, there could also be a fortuitous presence of these two disorders in the same patient (Figure 1). It has been argued that the revised diagnostic criteria, given by Del Brutto et al, do not seem to be reliable in differentiating between the enhancing lesions of neurocysticercosis and CNS tuberculosis. This distinction is an important issue because single cysticercus granuloma is a benign and self-limiting condition whereas tuberculoma is an active infection that requires prolonged therapy with potentially toxic drugs.

Tuberculoma Versus Cysticercus Granuloma

Rajshekhar et al made an attempt to differentiate between these two entities on the basis of clinical and imaging features, and subsequently, on the basis of this study and

Table 2: Revised diagnostic criteria of neurocysticercosis (Del Brutto et al)

<table>
<thead>
<tr>
<th>Category</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Absolute</td>
<td>1. Histological demonstration of parasite.</td>
</tr>
<tr>
<td></td>
<td>2. CT or MRI showing cystic lesions with scolex.</td>
</tr>
<tr>
<td></td>
<td>3. Fundoscopic visualization of parasite.</td>
</tr>
<tr>
<td>Major</td>
<td>1. Lesions suggestive of neurocysticercosis on CT or MRI.</td>
</tr>
<tr>
<td></td>
<td>2. Positive serum EITB.</td>
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<td></td>
<td>3. Resolution of cyst after therapy.</td>
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<td></td>
<td>4. Spontaneous resolution of single enhancing lesions.</td>
</tr>
<tr>
<td>Minor</td>
<td>1. Lesions compatible with neurocysticercosis on CT or MRI.</td>
</tr>
<tr>
<td></td>
<td>2. Suggestive clinical features</td>
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<tr>
<td></td>
<td>3. Positive CSF ELISA.</td>
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<tr>
<td></td>
<td>4. Cysticercosis outside CNS.</td>
</tr>
<tr>
<td>Epidemiologic</td>
<td>1. Household contact with Taenia solium infection.</td>
</tr>
<tr>
<td></td>
<td>2. Immigration from or living in an endemic area.</td>
</tr>
<tr>
<td></td>
<td>3. Travel to an endemic area.</td>
</tr>
</tbody>
</table>

| Definite: | One absolute; or two major + one minor + one epidemiologic. |
| Probable: | One major + two minor; one major + one minor + one epidemiologic; three minor + one epidemiologic. |
| Possible: | One major; two minor; one minor + one epidemiologic. |
their experience, Rajsekhar and Chandy noted that cysticerci are usually round in shape, 20 mm or less in size, and with ring enhancement or visible scolex, and cerebral edema severe enough to produce midline shift or focal neurological deficit is not seen. Tuberculomas are usually irregular, solid and greater than 20 mm in size. They are often associated with severe perifocal edema and focal neurological deficit. (Table 3). Regarding the diagnostic criteria of solitary cysticercus granuloma given by Rajsekhar and Chandy, there are several points which need attention. For example, in none of the studies has it been demonstrated that a lesion greater than 20 mm in size, irregular in shape, or with severe perifocal edema, in patients with new-onset seizures, will not disappear spontaneously. Moreover, no histopathological study has ever demonstrated that all large lesions (>20 mm) are tuberculomas and nothing else. On the contrary, every retrospective and prospective follow-up study of single enhancing CT lesions in patients with new-onset seizures observed the spontaneous resolution of the lesions irrespective of their size, shape and amount of surrounding edema.13,16 Another important point is that, in none of these series worsening (enlargement of CT lesion and appearance of new symptoms or focal deficit) has been noted though such a fear has always been expressed. 13,14 In fact, several series which included patients with CT lesions of varied sizes, shapes and perifocal edema, identical favorable clinical and radiological courses were obtained.15 Furthermore, in some series, small single enhancing CT lesions were treated with antituberculous treatment with excellent results17-19 and this adds to the controversy of the etiology of single enhancing CT lesions. Even if a patient does not fulfill the diagnostic criteria given by Rajsekhar and Chandy, it does not comprehensively exclude the possibility of a cysticercal etiology, and vice versa. In addition to the features suggested by Rajsekhar and Chandy (Table 3), several other differentiating imaging features have been suggested from time to time. For example, in this setup "target lesions" (lesions with central nidi of calcification or a dot enhancement) are frequently encountered. Earlier, target lesions were considered a pathognomonic feature of CNS tuberculosis. 20 Del Brutto et al and some other authors reported that visualization of an enhancing or a calcified eccentric dot which represented the scolex, could be considered a definite imaging feature of cysticercus etiology. 5,21,22 Unfortunately, histopathological evaluation of these target lesions is not available.

### Changes suggested in existing diagnostic criteria for Indian patients

In this article, a few changes in the diagnostic criteria given in Table 2 are being suggested, these changes are based upon the Indian experience along with the feasibility and availability of various diagnostic tests, which are needed to diagnose neurocysticercosis. In the proposed modifications, initial three categories of previous criteria by Del Brutto et al have been included. These categories include absolute, major and minor; again stratified on the basis of their respective diagnostic strength.6 Epidemiological criteria are irrelevant for Indian patients. Instead, a new section "diagnosis with caution" needs to be added (Table 4). In a later section certain neurological conditions, which are frequently associated with similar clinical and imaging pictures, have been considered. For example, in a human immunodeficiency virus (HIV) infected patient a ring enhancing CT/MR lesion is more likely to be a manifestation of toxoplasmosis rather than neurocysticercosis. So, on the background of HIV infection, a diagnosis of neurocysticercosis needs a great deal of caution. Keeping all these points in mind, the following changes are suggested in the criteria given by Del Brutto et al.6

### Table 3: Diagnostic criteria for cysticercus granuloma (Rajsekhar and Chandy) 12

**Clinical Criteria**
1. Seizure (partial or generalized) as initial symptom.
2. Absent persistent raised ICT.
3. No progressive neurological deficit.
4. No active systemic disease.

**CT Criteria**
1. Solitary, contrast enhancing lesion.
2. Lesion 20 mm in diameter.
3. Absence of severe cerebral edema (no midline shift).

### Table 4: Proposed modifications in the diagnostic criteria of neurocysticercosis (modified from Del Brutto et al) 6

**Absolute:**
1. Histological demonstration of parasite
2. Multiple small cystic lesions on CT or MRI with or without presence of scolex.

**Major:**
1. Presence of other types of characteristic cysticercal lesions on CT or MRI*
2. Spontaneous resolution or eventual calcification of intracranial lesions.
3. Positive serum EITB**

**Minor:**
1. Presence of characteristic clinical picture***
2. Positive CSF ELISA****
3. Aggravation of existing symptoms or appearance of new symptoms following treatment with anticysticercal drugs.
4. Evidence of cysticercosis outside the CNS.

**Diagnosis with caution:**
1. Old patient
2. HIV infected persons
3. Patient with pre-existing systemic tuberculosis or malignancy
4. Patient with grossly abnormal neurological examination

**Definitive:**
1) One absolute; 2) two major + one minor.

**Probable:**
1) One major + two minor; 2) three minor.

* Single or multiple ring/disk enhancing lesions and single or multiple calcified lesions.

** Electro-immuno transfer blot assay.

*** Most characteristic clinical manifestation is seizures.

**** Enzyme-linked immunosorbent assay.

***** X-ray Chest, Cerebrospinal fluid examination, ELISA for HIV infection, serological tests for other infections and abdominal sonography may be done, as per need, in a particular patient
**Absolute Criteria**

In the modified version of the diagnostic criteria there may be two items under absolute criteria:

**Histopathological demonstration of the parasite in the tissues obtained from the biopsy of a brain or spinal cord lesion**

Visualization of the parasite or parasite parts like the scolex with suckers and hooks identifies the lesion as a cysticercus. Even the biopsy of a calcified lesion may reveal evidence of body parts or whole body of a parasite in the nodule. Beyond doubt, whenever performed, this is the most unequivocal evidence of neurocysticercosis.

**Multiple cystic lesions with or without scolex on CT or MRI**

In the latest criteria by Del Brutto et al only cystic lesions showing scolex have been considered as absolute diagnostic criteria. Multiple, small, circumscribed, non-enhancing cystic lesions even without the evidence of scolex, do not have any possibility other than neurocysticercosis, so this point may be included as an absolute criterion (Figure 2). The scolex is visualized as a bright extramural nodule within the cyst and MR imaging is much more helpful for its demonstration. CT is less sensitive for scolex demonstration. So, better criteria for Indian patients will be the demonstration of multiple, small non-enhancing cystic lesions for which imaging with less expensive CT scan is sufficient.

**Major Criteria**

**Lesions highly suggestive of neurocysticercosis in neuroimaging studies**

In this item the lesions which will be considered characteristic for neurocysticercosis, include single or multiple enhancing CT/MR lesions and single or multiple small-calcified nodules. Single cystic lesions in the subarachnoid space, ventricles of the brain or even in cerebral parenchyma are uncommon manifestations in Indian patients with neurocysticercosis, moreover, these cystic lesions are often confused with congenital arachnoid cysts and epidermoid tumors.

In India, solitary cysticercus granuloma account for 60% of cases of neurocysticercosis (Figure 3). In one histopathological study, it has been observed that the majority of single CT lesions (25 out of 51 brain biopsies) had evidence of cysticercosis, however some of these lesions (6 out of 51) had definite tuberculoma. As has been mentioned earlier, one of the major drawbacks of the international criteria of Del Brutto et al, is the inability to differentiate cysticercus granuloma from tuberculoma. The problem of differentiation between cysticercus granuloma and tuberculoma becomes even more complicated for patients having multiple enhancing CT/MR lesions. The list of other differential diagnoses is long which includes multiple secondary cerebral malignancies and multiple pyogenic brain abscesses. No histopathological evidence is available from India to suggest that multiple enhancing CT/MR lesions are caused by cysticercus granuloma.

**Spontaneous resolution or eventual calcification of the lesion**

Is a good point in favor of neurocysticercosis because these events are consistent with the natural course of a cysticercal lesion. The problem with these criteria is that one will have to wait for several months or even a year before applying them, and diagnosis is made retrospectively.

In this revised scheme, the criteria based on the resolution of intra cranial cystic lesions, after therapy with albendazole or praziquantel, have not been included because data on untreated patients indicate that most of the lesions caused by neurocysticercosis either resolve spontaneously or eventually calcify. Moreover, in Indian randomized series involving multiple cystic lesions or single enhancing CT lesions, treatment with albendazole has not demonstrated any efficacy.

In another example, Kojic and White described a case with a single band at 50 KDa on EITB (positive test) and neuroimaging abnormali-
ties suggestive of neurocysticercosis. Autopsy findings excluded neurocysticercosis; CT lesion was because of poorly differentiated multifocal rhabdoid tumor. Access to EITB in India is limited.

**Minor criteria**

*Presence of a characteristic clinical picture*

Neurocysticercosis is characterized by varied clinical manifestations. There is no distinct clinical picture of neurocysticercosis. Several large series have shown that seizures, focal deficits, increased intracranial pressure, and intellectual deterioration are the almost equally common clinical manifestations. In India the overwhelming majority of patients present with seizures, other clinical manifestations are distinctly uncommon.

*Positive CSF ELISA*

In India, the ELISA test is extensively used for the diagnosis of cysticercosis. However, recent studies on serum have demonstrated a large number of false positive and false negative results. In contrast, ELISA using CSF was 87% sensitive and 95% specific, and remains a useful supportive tool for the diagnosis.

*Cysticercosis outside the CNS*

Del Brutto et al argued that in an endemic region a patient might have extra-CNS cysticercosis and neurological manifestations due to an unrelated cause. Therefore, a probable or even a definitive diagnosis of cysticercosis outside the CNS provides circumstantial evidence in favor of neurocysticercosis. However, in the presence of suggestive lesions of neurocysticercosis in the brain along with the presence of cysticercosis outside the CNS confirms the diagnosis. Definitive diagnosis of extra-neural cysticercosis will require one of the following: a) histopathological demonstration of parasite from excisional biopsy of a subcutaneous nodule. Demonstration of larval parts (hooks, suckers etc.) by fine needle aspiration cytology may provide a satisfactory alternative to open biopsy, b) plain X-ray films showing multiple "cigar-shaped" calcifications in the arm, thigh and calf muscles (Figure 4); c) direct visualization of a cysticercosis larva in the anterior chamber of the eye with ultrasonography. In India, a cysticercal lesion in the eye is frequently encountered in one of the extraocular muscles.

*Aggravation of existing symptoms or appearance of a new symptom following anticyticercal therapy*

If a patient with suspected neurocysticercosis develops a new symptom or if there is aggravation of existing symptoms, it gives a clue to cysticercal etiology. For example, Flisser et al reported a previously asymptomatic patient in whom neurological manifestations appeared after a single taenicial dose of praziquantel due to acute inflammatory changes in an occult intracerebral lesion. The appearance of headache, nausea, vomiting and recurrence of seizures are common during or after anticyticercal treatment. Patients with a subarachnoidal form of cysticercosis may develop cerebral infarction due to inflammatory vasculitis during the course of anticyticercal therapy. Rajshekhar noted that the occurrence of side-effects of albendazole therapy indicate the cysticercal nature of the lesion.

**Diagnosis of neurocysticercosis with caution in the presence of certain conditions**

This section is an important feature of the proposed modifications in the existing diagnostic criteria of neurocysticercosis. Whenever the diagnosis is not based upon absolute diagnostic criteria, the diagnosis of neurocysticercosis should be made af-
ter considering certain conditions given as follows:

**Old age**

Single enhancing CT lesions, seen in India, are common in children and younger patients. Chopra et al\(^\text{13}\) observed that 78% of 122 patients of their series were between 11 and 20 years of age. Sethi et al\(^\text{39}\) noted that approximately 46% of 186 patients were below 15 years of age. In this series only one patient was over 60 years of age. Epidemiological data about multiple enhancing CT lesions are not available. Because of the higher incidence of systemic malignancies in middle-aged and old persons, all single or multiple enhancing CT/MR lesions presenting with new-onset seizures should be seen with great suspicion for intracranial metastasis and an effort should be made to detect the primary site. Imaging characteristics of cerebral metastasis are not specific and often it is difficult to differentiate from other causes of enhancing CT lesions.

**Patients with pre-existing systemic tuberculosis or malignancy**

In the presence of either of these two conditions the diagnosis of neurocysticercosis in patients with single or multiple enhancing lesions is difficult to make. Intracranial tuberculomas were common intracranial masses in India and constituted approximately 10-20% of all intracranial space-occupying lesions. Similar enhancing lesions were frequently observed in patients with tuberculous meningitis. A favorable response to empirical antituberculous treatment provided additional support for tuberculous etiology.\(^\text{17,40}\) In a series of 186 patients with single enhancing CT lesions, 24 patients had active systemic tuberculosis and an additional 11 had a history of tuberculosis in immediate family contacts.\(^\text{39}\) No such data are available for multiple CT lesions. Garg et al reported an interesting patient—the patient had new-onset seizures, multiple non-tender subcutaneous nodules and multiple nodular enhancing CT/MR lesions (Figure 5). All these features were consistent with the diagnosis of neurocysticercosis, however, serological tests, CSP examination, histopathological examination of the subcutaneous nodule established tuberculous etiology. This patient responded very well to antituberculous drugs.\(^\text{41}\)

Among systemic malignancies cancers of the lung and breast are the most common causes of cerebral metastasis. Malignant melanoma has the greatest propensity to metastasize to the brain. Approximately one-third of patients presenting with brain metastasis do not have a known underlying cause.\(^\text{42,43}\)

**HIV infection**

Toxoplasmosis is the most common cause of enhancing CT/MR lesions in patients with AIDS. Lanjewar et al,\(^\text{44}\) in an autopsy study, diagnosed toxoplasmosis in 10 (more than 20%) of the 49 cases who died because of AIDS. Diagnosis of toxoplasmosis is usually made by positive toxoplasma antibody titre and clinico-radiological improvement following antitoxoplasma treatment. Toxoplasma lesions preferably involve subcortical structures such as the thalamus, basal ganglia and cerebellum, while in neurocysticercosis, the lesions are characteristically located at the cortical-subcortical interface. Primary CNS lymphoma occurs in up to 2% of patients.\(^\text{45}\) Various fungal granulomas can also present with single or multiple enhancing CT/MR lesions (Figure 6). In several case reports the association of neurocysticercosis and HIV infection has also been demonstrated. In a recent review Garg and Kar collected reports of 8 HIV infected patients who had neurocysticercosis. In the majority of patients neuroimaging revealed parenchymal hypodense cystic lesions of neurocysticercosis, because of this reason diagnoses were not difficult.\(^\text{46}\)

**Grossly abnormal neurological examination**

Abnormal neurological examination (e.g. hemiplegia) in Indian patients with neurocysticercosis is very uncommon, so, in
the presence of progressive focal deficit or other abnormal neurological findings the diagnosis of neurocysticercosis should be seen with suspicion. Tuberculomas, secondaries and cerebral abscesses are more frequently associated with focal neurological deficits.\(^{42,43}\) In a series of 60 patients of cerebral metastasis of unknown primaries, Srikanth et al noted that raised intracranial pressure and focal neurological deficits were the most common presenting features.

**Conclusion**

Available international diagnostic criteria are more suited to diagnose neurocysticercosis in developed countries where it is uncommon, and also other infective conditions with similar clinical and radiological features, like CNS tuberculosis, are equally uncommon. The diagnostic criteria given by Del Brutto et al are less suited for Indian patients of neurocysticercosis. There is a need to revise them again, so that they can become acceptable globally.

**References**