

Review Article

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Neurocysticercosis: Diagnostic problems & current therapeutic strategies

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Neurocysticercosis (NCC) is the most common single cause of seizures/epilepsy in India and several other endemic countries throughout the world. It is also the most common parasitic disease of the brain caused by the cestode *Taenia solium* or pork tapeworm. The diagnosis of NCC and the tapeworm carrier (taeniasis) can be relatively inaccessible and expensive for most of the patients. In spite of the introduction of several new immunological tests, neuroimaging remains the main diagnostic test for NCC. The treatment of NCC is also mired in controversy although, there is emerging evidence that albendazole (a cysticidal drug) may be beneficial for patients by reducing the number of seizures and hastening the resolution of live cysts. Currently, there are several diagnostic and management issues which remain unresolved. This review will highlight some of these issues.

Key words Brain - cysticercosis - diagnosis - epilepsy - taeniasis

Introduction

Neurocysticercosis (NCC) is the most common parasitic disease affecting the brain and is also the common identifiable cause of new-onset seizures in several regions of the world including India. In a community-based survey involving over 50,000 individuals in a district in Tamil Nadu in southern India, NCC was found to be the cause of active epilepsy (at least one seizure in the five years before the survey) in at least a third of the patients¹. Based on the results of this large survey, the prevalence of NCC as a cause of active epilepsy in India was calculated to be one per 1000 population. Thus, at least 1.2 million persons in India are suffering from active epilepsy due to NCC. The most common form of the disease in India was the solitary cysticercus granuloma (SCG) (first identified

in 1989) which was seen in up to 60 per cent of patients with NCC^{2,3}.

NCC, caused by the larval form of the cestode *Taenia solium*, is associated with lack of sanitation, poor hygiene and free roaming pigs. Local transmission of the disease is, however, only possible in the presence of an adult *Taenia* carrier in the gut. Taeniasis is caused only by the consumption of pork infected with cysticercosis, but NCC can also occur in vegetarians and non-pork eaters.

Although the disease can potentially be controlled if not eliminated, there are several socio-economic and healthcare-related issues that constitute barriers to this goal. The problems being faced by clinicians and researchers dealing with NCC include those

related to the diagnosis of NCC and taeniasis and their management. This review will address issues related to these problems.

Diagnostic problems

Taeniasis

Since a *Taenia* carrier is central to the local transmission of the disease, identifying such carriers is also crucial to any control programme. *Taenia* carriers are typically asymptomatic and, therefore, do not seek medical help. Moreover, the passage of gravid proglottids (the egg-bearing segments of the worm) in the stools of the carriers is intermittent and unpredictable. Unlike *Taenia saginata* carriers, *T. solium* carriers do not expel proglottids independent of defecation.

The methods available for diagnosing taeniasis are listed in the Table. The tests have variable sensitivity being low for stool microscopy and high for the coproantigen assay. In one study, microscopy detected 38 per cent of *Taenia* carriers whereas coproantigen test detected 98 per cent⁴. However, none of these tests except the species-specific enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction (coproPCR) distinguish between infection with *T. solium* and *T. saginata* (the latter, beef tapeworm, does not cause NCC).

Confirmation of a positive coproantigen test is obtained by the retrieval of the worm following therapy with niclosamide (single dose of 2 g orally) and a purge⁴. One of the major problems with the coproantigen test has been the issue of false positivity. In the initial field trials of the coproantigen test, 12 of the 79 positive individuals did not expel the worm after

treatment and were classified as being false positive⁴. In a study on taeniasis conducted in Vellore district, we found that only two of 10 coproantigen-positive persons expelled the worm following treatment⁵. Explanations for these false positive results include the presence of immature worms in the gut and reactivity to other unknown antigens⁶. Efforts at developing more sensitive and specific tests for taeniasis include a species-specific coproantigen test, a serum antibody test and a coproPCR test⁷⁻⁹. However, none of these have been validated in large field trials. Since none of the advanced tests including the coproantigen test is commercially available, the low sensitivity microscopy remains the most readily accessible test for the diagnosis of taeniasis.

Neurocysticercosis

Clinical features: NCC can cause non-specific symptoms such as seizures, headache and focal neurological deficits which can be caused by a number of other pathologies. Hence, there are no specific symptoms or signs that are diagnostic of NCC. Only a rare finding of a live cysticercal cyst seen on fundoscopy in the retina or vitreous of patient with suspected NCC can be considered diagnostic. All patients presenting with new-onset seizures, especially if the seizures are focal with or without secondary generalization should be suspected to have NCC. A search should be performed for any subcutaneous nodules which could indicate subcutaneous cysts, although this finding is rare in those with a single granuloma. Thus, a diagnosis of NCC will require other tests.

Neuroimaging: The mainstay of diagnosis of NCC is neuroimaging using contrast enhanced computerized tomography (CECT) or magnetic resonance imaging (MRI). Both these imaging techniques are expensive, relatively inaccessible to several people in endemic regions and require the use of contrast agents which might have side effects. CT scan is preferred for identifying parenchymal calcifications while MRI is the preferred modality for parenchymal lesions which are in the temporal lobe and frontal lobe close to the skull base, intraventricular cysts and subarachnoid cysts. For patients with SCG, a well performed thin slice CECT scan is as good as an MRI in the detection of the granuloma¹⁰.

While CT and MRI will almost invariably identify the NCC lesions, there may be diagnostic difficulties in differentiating NCC from other lesions of the brain such as tuberculomas, other parasitic cysts such as

Table. Diagnostic tests for taeniasis and neurocysticercosis

Taeniasis
Microscopic stool examination for ova
Coproantigen assay
Species specific coproantigen assay
Serum antibodies against Taenia antigens
Neurocysticercosis
ELISA
EITB
Serum antigen ELISA
Urine antigen ELISA
ELISA, enzyme linked immunosorbent assay; EITB, enzyme linked immunotransfer blot

hydatid cysts, neoplastic lesions such as gliomas and metastatic lesions. The diagnosis of NCC on imaging is considered to be secure when there is a cystic lesion with an eccentric 'dot' representing the scolex. In CT, the scolex is usually hyperdense, and on T2-weighted MR images, it appears hypointense (dark). Most patients with multiple NCC lesions in the brain parenchyma will show lesions at different stages of involution. Therefore, there will be live cysts, granulomas and calcific lesions, all seen in the same brain. Intraventricular cysts are usually live cysts with a thin wall and can be notoriously difficult to image on CT scan as the density of the cyst fluid is identical to that of the surrounding cerebrospinal fluid (CSF). Since the cyst wall is thin and does not usually enhance with contrast injection, the cyst does not stand out from the surrounding CSF. On MRI using heavily T2 weighted sequences (constructive interference in a steady state or driven equilibrium), intraventricular cysts are easier to identify especially if the scolex is visible (Fig. 1). These special MR sequences utilize the subtle differences in the intensity of the CSF and the cyst fluid to show up the cyst¹¹.

There are similar problems in imaging of subarachnoid cysts on CT scans where small cysts will not be distinguishable from the normal subarachnoid cisterns such as sylvian, cerebellopontine angle, suprasellar and prepontine cisterns¹². Larger subarachnoid cysts can be suspected by asymmetric enlargement of these cisterns, but the cysts themselves are difficult to visualize on the CT scan. Special MR sequences used to identify the intraventricular cysts

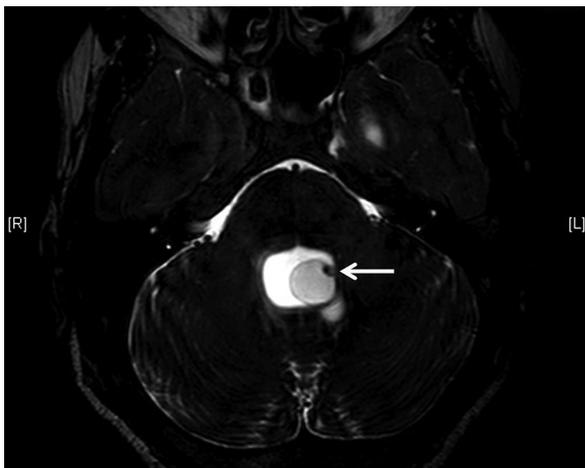


Fig. 1. A driven equilibrium sequence axial magnetic resonance image showing a fourth ventricular cysticercal cyst with the scolex seen as a hypointense (dark) dot (arrow).

most often are useful in identifying the subarachnoid cysts. As mentioned above, MRI might miss small parenchymal calcifications unless susceptibility weighted imaging is used.

Immunological tests: Serum is usually tested for the diagnosis of NCC both because of the relative ease of obtaining the sample and also because of some methodological issues; some tests such as the enzyme linked immunotransfer blot (EITB) perform better with serum than with CSF¹³. As of now, EITB is the best serological test available for the diagnosis of NCC. This assay tests for antibodies to seven larval specific antigens. It has a sensitivity of 98 per cent and specificity of 100 per cent in patients with more than one live cyst or subarachnoid disease¹³. However, it only detects the presence of antibodies to the larval antigen and does not necessarily indicate the presence of active disease. Hence, it may be positive in persons with exposure to the parasite antigen (seropositive), those with past treated disease (antibodies may persist up to one year after successful treatment) and those with disease outside the brain¹⁴. There will be a large number of asymptomatic persons in endemic regions who are seropositive with the EITB but do not have the disease. In a study performed by our group, the seroprevalence (those with positive EITB) was over 15 per cent in a large sample of asymptomatic persons residing in Vellore district¹⁵. EITB is, however, very specific and does not cross-react with other parasites¹⁵. In individual patients suspected to have NCC on neuroimaging, a positive EITB can be considered to confirm the diagnosis especially if the individual resides in a non-endemic region. EITB is almost always positive in patients with multiple non-calcified parenchymal lesions, intraventricular and subarachnoid NCC but has a low sensitivity in patients with SCG (around 60%) and is frequently negative in patients with solitary calcific parenchymal lesions¹⁶⁻¹⁸. The sensitivity of EITB was enhanced in patients with SCG by nearly 50 per cent by modifying the *T. solium* glycoproteins using urea¹⁹.

The antigen ELISA (Ag-ELISA) detects the presence of circulating larval antigens in serum and hence, more likely to be associated with the presence of active disease in a person^{20,21}. It is almost always positive in patients with subarachnoid disease but like the EITB, is likely to be negative in those with calcific lesions and with one or two parenchymal lesions. Even in those with more parenchymal lesions, its sensitivity

is poor and ranges between 72 and 86 per cent¹⁴. However, the Ag-ELISA could be used to monitor the effects of therapy as its levels fall rapidly following successful therapy²². Asymptomatic persons can also test positive for the Ag-ELISA and on long term follow up remain asymptomatic²³.

Urine antigen detection ELISA has been used by some workers to avoid the discomfort of obtaining a serum sample in field studies^{24,25}. The sensitivity was around 90 per cent in patients with more than one cyst in the brain.

One of the major problems in using immunological tests in clinical practice is that the tests are not easily available commercially and when available are expensive costing around ₹ 15,000 - 20,000 per patient for the commercial EITB test⁵. The performance of the commercial kits can also be variable as the larval antigens used in the kits are not indigenous.

Diagnostic criteria: Since no single test can definitively diagnose NCC, except by brain biopsy, diagnostic criteria are necessary. In 1993, diagnostic criteria were proposed for the diagnosis of SCG and were validated in a prospective study in 1997, involving 401 patients presenting with seizures and a solitary brain mass on the CT scan (215 with SCG)^{26,27}. SCG diagnostic criteria have sensitivity of 99.5 per cent, specificity of 98.9 per cent, positive predictive value of 99 per cent, negative predictive value of 99.5 per cent and likelihood ratios for the positive and negative tests of 92.99 and 0.005²⁷. The high likelihood ratios ensure that the criteria will perform well even in regions of the world where the disease is not endemic, and therefore, the prevalence rates are low.

In 2001, an international experts group proposed diagnostic criteria for NCC in general with a set of absolute, major, minor and epidemiological criteria based on which a patient suspected to have NCC could be diagnosed with definitive or probable NCC²⁸. The criteria rely on histological evidence, clinical features, neuroimaging findings, results of immunological tests and exposure to the disease. The diagnostic criteria for SCG have been incorporated in the NCC diagnostic criteria as major criteria. However, the NCC diagnostic criteria have not been validated and have faced some criticism^{29,30}. Notwithstanding the criticism, these diagnostic criteria remain the best available resource to clinicians worldwide when confronted with a patient with suspected NCC³¹.

Diagnostic problem: special situations: One of the common clinical situations in our country when the diagnosis is difficult is a patient who presents with seizures and raised intracranial pressure with neuroimaging showing multiple small enhancing granulomas all over the brain with associated oedema (Fig. 2). The images do not reveal calcifications, live cysts, intraventricular or subarachnoid cysts. In this situation, the differential diagnosis includes NCC and tuberculomas. Usually, EITB will be positive in the serum, but in an endemic country like India, EITB can be positive due to exposure to the larval antigen and not due to established disease. Therefore, a positive EITB in this situation may not necessarily indicate a definitive diagnosis of NCC. A brain biopsy may sometimes be necessary to establish a definitive diagnosis.

Current therapeutic strategies

The mainstay of treatment of a patient with NCC involves symptomatic therapy. Since most patients with NCC present with seizures, antiepileptic drugs (AEDs) are to be used. Steroid therapy may be needed to control oedema associated with the lesions. Dexamethasone or prednisolone is commonly used for short periods of a few days or weeks. As NCC presents with varied symptoms depending on the location of the cyst and the stage of degeneration, the treatment also varies. For an overview of the suggested management of different forms of NCC, a consensus statement of a

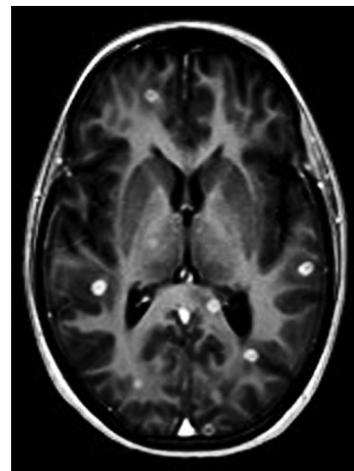


Fig. 2. Multiple small ring enhancing lesions in a patient presenting with headache and seizures. Enzyme linked immunotransfer blot for cysticercal antibodies in serum was positive. As only granulomas were seen without any of the other stages of the cysts (live and calcific), the patient was treated with anti-tuberculous therapy with resolution of the granulomas. A brain biopsy would be the only method to confirm the diagnosis.

group of international experts is available³². In a later paper, some of the issues pertaining to the treatment of NCC and research needs arising thereof have been dealt with³³. In the present review, the discussion will be limited to a few specific issues and does not cover the therapeutic strategies for the entire spectrum of NCC. An attempt has been made to provide information obtained from randomized controlled trials (RCTs).

Debate over benefits of cysticidal drugs

Ever since cysticidal drugs were introduced for NCC in the late 1970s (praziquantel) and 1980s (albendazole), it has been a matter of debate as to whether hastening the destruction of the cysts in the brain is symptomatically beneficial to the host or not. While intuitively it might seem that destroying the parasite should benefit the host, it should be recognized that the symptoms of NCC arise from the spontaneous involution or destruction of the parasite¹⁴. The host inflammatory reaction that accompanies the parasite's death appears acutely in the form of brain oedema around the parasite and release of inflammatory cytokines and chronically in the formation of a gliotic scar. These events, acute and chronic, could lead to symptoms such as those of raised intracranial pressure (due to oedema), seizures (due to the release of cytokines and other neurotoxic agents) and a chronic epileptic scar. This is the basis for the argument against administration of cysticidal drugs³⁴.

In recent years, several RCTs and meta-analysis have attempted to provide a definitive answer to the question: Does cysticidal drug therapy benefit the patient? However, a final, conclusive answer continues to evade us.

Cysticidal drugs and steroids in patients with solitary cysticercus granuloma

Since the early studies showing a possible benefit of the use of albendazole in hastening the resolution of persistent SCG³⁵, there have been several RCTs³⁶⁻⁴⁰ and one pseudo randomized control trial⁴¹ evaluating the effect of albendazole in patients with SCG. The effects of albendazole (15 mg/kg/day for 7-14 days) and steroids on seizure outcome and lesion resolution in patients with SCG were usually studied. Unfortunately, most of the RCTs have methodological flaws and all of them report outcomes at a relatively short follow up of less than 12 or 18 months. Meta-analyses based on these RCTs have concluded that there is modest evidence that seizure outcome is better in patients prescribed albendazole^{42,43}. Lesion resolution also might be faster

with the administration of albendazole, but this effect is not clear. Steroids alone did not seem to offer the benefits that were seen with albendazole therapy. However, steroids are usually administered with albendazole to reduce the side effects associated with cysticidal drug therapy. It has also been reported that albendazole therapy does not reduce the calcification rate of around 20 per cent in patients with SCG^{42,43}. Thus, it is likely that long-term seizure recurrence rates might not benefit with albendazole as calcification is a major risk factor for seizure recurrence. The only possible downside to routine administration of albendazole to all patients with SCG is the occurrence of side effects in a substantial proportion of patients⁴⁴. As there is modest evidence of benefit, albendazole is recommended for patients with SCG at initial presentation⁴⁵.

Cysticidal drugs for patients with multilesional neurocysticercosis

One trial reported a 50 per cent reduction in generalized seizures but not all seizures in patients with multilesional NCC [patients with 1-20 viable cysts (live and degenerating) in the brain] treated with albendazole⁴⁶. However, there was no significant reduction in the total number of seizures in the treated group. Another RCT did not find a reduction in seizure numbers or enhanced cyst resolution in the treated group⁴⁷. Similar to the case with SCG, albendazole does not seem to reduce the incidence of calcification in patients with multilesional NCC. Most studies using albendazole have, however, reported a higher rate of lesion resolution when compared to placebo. Therefore, while albendazole appears to destroy larvae, it does not have a profound beneficial effect on seizure outcome and seizure recurrence.

In a recent RCT, 10 days combined therapy with albendazole (15 mg/kg/day) and praziquantel (50 mg/kg/day) was found to be superior to either albendazole alone or high dose albendazole (22 mg/kg/day) in clearing cysts from the brain⁴⁸. Cyst resolution, at six months after treatment, was noted in 64 per cent of patients in the combined therapy group versus 39 per cent in the standard albendazole therapy group. Furthermore, there was no difference in the side effects in the three groups. Thus, combined therapy seems to be good option in patients with multilesional NCC.

Duration of antiepileptic drugs

Most patients with SCG present with a few seizures which are easily controlled with a single AED. AEDs should be continued till the granuloma has resolved on

follow up imaging. Once the granuloma has resolved, AEDs can be withdrawn gradually provided the patient has not had a seizure in the past three months. The risk of recurrent seizures after withdrawal of AEDs in patients with a resolved SCG has been studied in a large cohort of patients followed up for 2-10 yr (mean follow up 76.2 months)⁴⁹. Recurrent seizures occurred in 15 per cent of patients with most seizures occurring in the first three months after withdrawal of AEDs. Risk factors for recurrence were found to be >2 seizures during the disease, breakthrough seizures (seizures occurring after starting AEDs) and most importantly the presence of a calcific residue on the follow up CT scan. Patients with any of these risk factors or more than one risk factor should be advised to continue AEDs for a longer duration (1-2 years). However, for patients with multilesional NCC, AEDs are needed for several years in over 50 per cent of patients as most of these patients are prone to recurrence of seizures following withdrawal of AEDs^{50,51}. Like for SCG, calcification is a major risk factor for recurrence of seizures^{50,51}.

Endoscopic surgery for intraventricular cysts

Intraventricular cysts are one of a few surgical indications in patients with NCC⁵². In the last two decades, endoscopic excision of intraventricular cysts has become the procedure of choice as opposed to the open craniotomy and microsurgical excision that was used earlier^{53,54}. Endoscopic surgery is minimally invasive being achieved through a single burr hole. It can often be curative if there is a single cyst in the ventricle. The side effects of the surgery are minimal when performed by experienced surgeons. Although there was concern regarding possible anaphylactic reactions to the rupture of a cyst during surgery, these have been proven to be misplaced as no such reactions have been reported in spite of cysts being routinely ruptured during excision.

Conclusions

Highly sensitive, specific and cost-effective tools for the diagnosis of taeniasis and NCC are lacking although progress has been made in the development of immunological tests for both in the last two decades. Expensive neuroimaging is still central to the diagnosis of NCC. The management of NCC is debated especially with respect to the use of cysticidal drugs as their benefits have not been conclusively proven. There are several other management issues awaiting resolution.

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Conflicts of Interest: None.

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