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Neurocysticercosis: Clinical Feature, Diagnostic and Current therapeutic Strategies

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Abstract **Review Article**

Background: Neurocycticercosis is the most common parasitic disease of the central nervous system caused by larval forms (cysticercus cellulosae) of cestode tapeworm, taenia solium. It is the most common cause of focal seizure in india and several other endemic countries. Despite Several Immunologic test, neuroimaging remain the main diagnostic test. Seizure is the most common clinical manifestation of neurocysticercosis. There is also controversy regarding management of seizure but there is emerging evidence that albendazole may be beneficial for patient by reducing the no. of seizure. ***Material and Method:*** All cases aged more than 12 yrs admitted in dept. of neurology or attending Neurology OPD, JAH and GRMC, Gwalior are the subjects of the study. ***Conclusion:*** Focal Seizures are the most common clinical manifestation of neurocycticercosis. Seizures are reported to occur in 70 to 90% of patients with neurocysticercosis. Other symptoms include headache and focal neurological deficits. The lesions of neurocysticercosis can present as single or multiple, although multiple is less common. The single cyst infection (47.7% - 53.4%), is the most common manifestation in Indian subcontinent. Diagnosis is done by clinical, radiological and immunological methods. Serological diagnosis is done by complement fixation test, indirect haemagglutination tests and ELISA. A newer gold standard test is enzyme linked immunoelectron transfer blot (ELITB) assay which is done with CSF or serum samples based on seven glycoproteins specific to the pathogen. Western blot assay have also been developed for diagnosis of NCC. Neuroimaging studies are done using MRI Brain which is used to differentiate various stages of the parasite. CT Brain is helpful to detect calcified lesion. Initial management of neurocysticercosis is done with albendzole and praziquentel. Antiepileptic drug will be given till granuloma has resolved on follow up imaging.

Keywords: neurocysticercosis, taenia solium, focal seizure,tuberculoma, anti epileptic drug, toxoplasmosis.

INTRODUCTION

Neurocysticercosis (NCC) is caused by an infection of the human CNS by the larval stage of the pork tapeworm, Taenia solium. Currently, It is the most common parasitic disease of the human CNS, NCC has become a major public health problem for most of the developing world, as well as in industrialized countries with a high immigration rate of people from endemic countries in Latin America, Asia, and Africa [1]. It is the most common cause of symptomatic epilepsy worldwide. Current estimates of the number of individuals with epilepsy due to NCC are 0.45– 1.35 million in Latin America, 1 million in India, and 0.31–4.6 million in Africa [2]. The prevalence of NCC as a cause of active epilepsy in India was calculated to be 1 per 1000 population [3]. 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 [4, 5].

NCC caused by larval forms (cysticercus cellulosae) of tapeworm, taenia solium. These cysts are situated in various areas like intracerebral, subarachnoid, intraventricular, spinal cord, and also in various organs, muscles and subcutaneous tissues outside the brain. The parenchymal cyst tends to remain dormant for several years where it can cause minimal or no symptoms. The four stages of parenchymal cysts are (1) vesicular, (2) colloidal, (3) granular-nodular and (4)

calcific [6]. The parasites are usually alive in the first two stages, while the last two stages represent the dead parasites. Patients become symptomatic only when the larva inside the cyst dies and releases its antigen, resulting in an intense inflammatory reaction.

CLINICAL FEATURE

Seizures are the most common clinical manifestation of neurocycticercosis[7]. Seizures are reported to occur in 70 to 90% of patients with neurocysticercosis[8]. Other symptoms include headache and focal neurological deficits. The lesions of neurocysticercosis can present as single or multiple, although multiple is less common. The single cyst infection (47.7% - 53.4%), is the most common manifestation in Indian subcontinent [9]. In my study out of 90 cases, 14 cases are of neurocysticercosis, which alone contribute approximately 16% out of all cases of focal seizure, Male to female ratio is 6:1 .Most of case of neurocysticercosis are present in between 21-50 year age group (9 out of 14). Most common type of seizure is focal seizure without dyscognitive feature, seen in 9 out of 14 cases, followed by focal seizure with secondary generalization seen in 5 out of 14 cases. No cases reported for focal seizure with dyscognitive feature.

DIAGNOSTIC PROBLEM

Diagnosis is done by clinical, radiological and immunological methods. Serological diagnosis is done by complement fixation test, indirect haemagglutination tests and ELISA. A newer gold standard test is enzyme linked immunoelectron transfer blot (ELITB) assay which is done with CSF or serum samples based on seven glycoproteins specific to the pathogen. Western blot assay have also been developed for diagnosis of NCC [10].

Diagnostic criteria for neurocysticercosis

Categories of Criteria	Criteria
Absolute	1. Histologic demonstration of parasite from biopsy of a brain or spinal cord, or 2. Cystic lesions showing scolex on CT or MRI, or 3. Direct visualization of subretinal parasites by funduscopic examination
Major	1. Lesions highly suggestive of neurocysticercosis on neuroimaging studies, or 2. Positive serum EITB for detection of anticysticercal antibodies, or 3. Resolution of intracranial cystic lesions after therapy with albendazole or praziquantel, or 4. Spontaneous resolution of small single enhancing lesions
Minor	1. Lesions compatible with neurocysticercosis on neuroimaging studies, or 2. Clinical manifestations suggestive of neurocysticercosis, or 3. Positive CSF ELISA for detection of anticysticercal antibodies or cysticercal antigens, or 4. Cysticercosis outside the CNS
Epidemiologic	1. Evidence of household contact with *T. solium* infection, or 2. Individuals coming from or living in cysticercosis-endemic area, or 3. History of frequent travel to disease-endemic areas

Definitive diagnosis: 1 absolute criterion, or 2 major +1 minor and 1 epidemiologic criterion; *probable diagnosis*: 1 major 2+ minor criteria, or 1 major 1+ minor and 1 epidemiologic criterion or 3 minor +1 epidemiologic criterion.
ELISA, enzyme-linked immunosorbent assay.

Tuberculoma versus cysticercus granuloma

It is very difficult to differentiate between these two entities on the basis of clinical and imaging features. On the basis of Rajshekhar and Chandy *et al.* [11] study, It was found that cysticerci are usually round in shape, 20 mm or less in size 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 [12].

Even if a patient does not fulfill the diagnostic criteria given by Rajshekhar and Chandy, it does not comprehensively exclude the possibility of a cysticercus etiology, and vice versa. In addition to the features suggested by Rajshekhar and Chandy (Table 1), several other differentiating imaging features have been suggested from time to time. For example, in this setup "target lesions" (lesions with central nidus of calcification or a dot enhancement) are frequently encountered. Earlier, target lesions were considered a pathognomonic feature of CNS tuberculoma [13]. 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; unfortunately, histopathological evaluation of these target lesions is not available.

Table-1: Diagnostic criteria for cysticercus granuloma (Rajshekhar and Chandy)

Clinical Criteria
1. Seizures (partial or generalized) as initial symotoms
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 oedema (no midline shift)

Diagnosis of Neurocysticercosis in some special condition

In some special Conditions the diagnosis of neurocysticercosis should be made after 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*. [14] observed that 78 % of 122 patients of their series were between 11 and 20 years of age. Sethi *et al*. [15] noted that approximately 46 % of 186 patients were below 15 years of age. In my study only one patient is above 60 year 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 anti tuberculous treatment provided additional support for tuberculous etiology. Garg *et al*. [16] reported an interesting patient-the patient had new-onset seizures, multiple non-tender subcutaneous nodules and multiple nodular enhancing CT/MR lesions. All these features were consistent with the diagnosis of neurocysticercosis, however, serological tests, CSF examination, histopathological examination of the subcutaneous nodule established tuberculous etiology. This patient responded very well to antituberculous drugs.

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 [17].

HIV infection

Toxoplasmosis is the most common cause of enhancing CT/ MR lesions in patients with AIDS. Lanjewar *et al*. [18]. 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 anti toxoplasma 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 [19]. Various fungal granulomas can also present with single or multiple enhancing CT/MR lesions. In several case reports, there is 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.

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.

Cysticidal drugs should be used or not

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 parasite [20].

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 drugs [21]. 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 SCG [22]. 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[23]. 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 [24].

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 patients.

As there is modest evidence of benefit, albendazole is recommended for patients with SCG at initial presentation [25].

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 albendazole[26].

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 group [27]. 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 brain [28]. 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[29]. 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 [30]. Like for SCG, calcification is a major risk factor for recurrence of seizures [31].

Endoscopic surgery for intraventricular cysts

Intraventricular cysts are one of a few surgical indications in patients with NCC [32]. 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 [33]. 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.

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