Chapter

112

Neurocysticercosis

RAVINDRA KUMAR GARG

INTRODUCTION

Neurocysticercosis is the commonest parasitic disease of central nervous system. It is caused by larvae of pork tapeworm *Taenia solium*. *Taenia solium* infection is a zoonotic disease and involves pigs and man in its life cycle.

EPIDEMIOLOGY

Taenia solium and neurocysticercosis infection is widely endemic in rural areas of all developing countries. It is also one of few conditions included by World Health Organization in the list of potentially eradicable infectious disease of public health importance. Recent World Health Organization data suggest that over 50,000 deaths each year occur due to neurocysticercosis and majority of these people belong to active epilepsy group. In India up to 50% of patients with seizure disorder have serological evidence of cysticercosis. Stools survey in India has shown prevalence of *Taenia* infestations varying from 1.11 to 3.9%, being higher in East India region. The incidence is 12-15% in labor colonies and slums areas where pigs are harbored. In the pre- computed tomography (CT) era, the frequency of neurocysticercosis as a cause of epilepsy in India was reported to vary from 2.2-9.6%. After the availability of newer imaging techniques, the neurocysticercosis has been found to be the cause of epilepsy in 10-18.6% of patients. Within the country, neurocysticercosis appears to be more prevalent in northern regions—Bihar, Uttar Pradesh and Punjab. Low prevalence of the disease is found in Kerala reflecting efficient sanitation, pig husbandry, a superior socio-economic and educational status. Low prevalence in Kashmir is because of religious reasons. In addition to poor sanitation, unhealthy pig rearing practices, low hygienic standards, and unusual customs such as consumption of raw pork is an additional factor contributing to the spread of the disease. Recently, cysticercosis has been recognized as an important parasitic disease in the United States[1-4].

ETIOLOGY AND PATHOGENESIS

Humans are the only definitive host for *Taenia solium*; pigs are the usual intermediate host. In the normal life cycle of *Taenia solium*, human hosts the 2-4 meter long adult tapeworm that resides in the upper part of intestine. The adult worm has a scolex and a large flat body composed of hundreds of proglottids. Proglottids are excreted into the faeces. The eggs in these proglottids are infective for both humans and animals. The eggs may survive in the environment for several months. After ingestion of eggs by the intermediate host (most often pigs), the eggs hatches to liberate hexacanth embryo (oncosphere) into the intestine. After penetrating intestinal wall, larvae lodge into various parts of body with predilection for striated muscles. These cysticerci can survive for months to years. The life cycle continues when humans eat undercooked pork that contains the viable cysticercus larva. Neurocysticercosis develops when humans become the intermediate host and when an individual ingests undercooked food or water that is contaminated with *Taenia solium* ova. The parasite may lodge in any body tissue in humans but show a predilection for the brain. Less common sites include the retina, heart, skeletal muscle, and subcutaneous tissue. In the brain, the parasites commonly lodge in small cerebral blood vessels located between the gray and white matter. The oncosphere then appears to burrow through the vessel wall into the adjacent brain

or into the leptomeninges. Oncospheres may also lodge in the meninges, ependyma, and choroid plexus of the ventricles. Involvement of the spinal cord is unusual.

The larva eventually develops into a cyst with a protoscolex surrounded by a bladder wall. At this early stage, the cyst is tiny (1 to 3 mm in diameter). The stage is often called the vesicular cyst stage. The living cyst evokes only a minimal surrounding inflammation and remains viable from 2 to more than 10 years, before the osmotic barrier of the cyst wall breaks down. At this time the clear cyst fluid thickens and becomes more opaque, the cyst wall thickens, and hyaline degeneration and mineralization begin. The cyst wall begins to leak *Cysticercus cellulosae* antigens, eliciting an intense inflammatory reaction in the adjacent brain. The immune response is both humoral and cell mediated. In response to the inflammation, fibroblasts may form a capsule-like structure surrounding the cyst. The degenerating cysts are called colloid cyst stage. The colloid cyst stage may persist for months to 1 to 2 years. At this stage, patients typically develop clinical symptoms. It is believed that the immunologic process elicited by the release of dying parasite antigens is responsible for clinical manifestations of neurocysticercosis. When the cysticercus dies, the bladder wall collapses to form a small granuloma. Months to years later some of these dead cysts become calcified (called the calcified phase or nodular calcified stage)[4-8].

CLINICAL MANIFESTATIONS

The clinical presentation of neurocysticercosis is varied and depends on the stage, number, size, and locations of the cysticercal cysts within the central nervous system and the host's immune response. The disease may remain asymptomatic. Seizures are the most common symptom occurring in 70-90% of patients having brain parenchymal cyst or calcification. Seizures are often generalized tonic-clonic, simple partial or complex partial type. A well-known complication of neurocysticercosis is cerebral arteritis, which is usually manifested by cerebral ischemia. Mostly these are in the form of an endarteritis involving the smaller basal vessels due to basal exudates. When cysticerci lodge within the ventricular system, life-threatening acute intracranial hypertension secondary to hydrocephalus may develop. Cysts in the subarachnoid space may invade the Sylvian fissure and grow to large sizes (giant cysts) causing intracranial hypertension with hemiparesis, partial seizures or other focal neurological signs. Racemose cysts in the basal cisterns can cause an intense inflammatory reaction, fibrosis and progressive thickening of the leptomeninges at the base of the brain. In approximately 60% of the cases, there is an obstruction of the cerebrospinal fluid circulation, resulting in hydrocephalus and intracranial hypertension[7-9]. Reversible dementia occurs in patients with untreated neurocysticercosis. It is reversible in most cases[10]. Spinal cysticerci most frequently involve the subarachnoid space resulting in radiculopathy, myelopathy, partial Brown Sequard syndrome or spastic paraparesis. Thoracic region is most often involved. Intramedullary cysticercosis develops via hematogenous route and presents as partial or complete transverse cord syndromes. Subcutaneous cysticerci are less common in India. Diffuse muscle involvement may result in pseudo-hypertrophic myopathy like picture. Rarely disseminated variety of neurocysticercosis has also been reported[7-9].

DIAGNOSTIC WORK UP

Computed Tomography

It has been shown that CT can image various evolutionary stages of the cysticercus from its first entry into the brain until its death. In vesicular stage the cranial CT scan shows one or more rounded circumscribed and hypodense areas of variable size without enhancement by contrast-media. After maturation of cysts, a hyperdense eccentric scolex may also be identified. At this stage there is no surrounding vasogenic edema. In colloidal stage ring/disk enhancing lesions are seen. There is often intense vasogenic cerebral edema. Ultimately lesions get calcified.

Calcified lesions are often small, rounded, homogenous hyperdense area, showing no enhancement after administration of contrast media. In disseminated cysticercosis a starry-night appearance is seen (Fig. 1). This is produced by the hypodense scolices of living cysticerci standing out against the lower attenuation density value of the brain. CT scan of muscles can also be used in the diagnosis of cysticercosis. A 'honeycomb' appearance produced by a large number of live cysticerci in pseudohypertrophic muscles has been described.

Magnetic Resonance (MR) Imaging

MR images a living parenchymatous cysts as a 5.20 mm diameter round lesions of cerebrospinal fluid (CSF) equivalent density on both T1 and T2-weighted images. An isodense to hyperdense scolex can be identified within most cysts producing a pea in the pod, appearance (Fig. 2). In the dying cysticercus the difference between scolex and cysts becomes unclear. The cyst fluid shows greater and increasing signal intensity than the

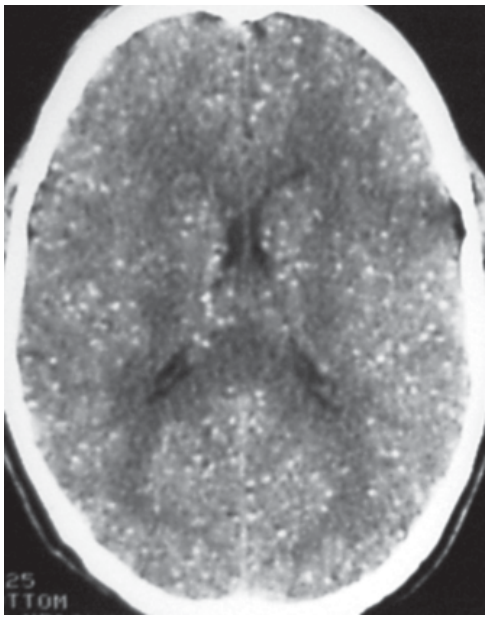

Fig. 1: CT of brain showing a "starry night appearance" in a patient of neurocysticercosis with massive parasitic load

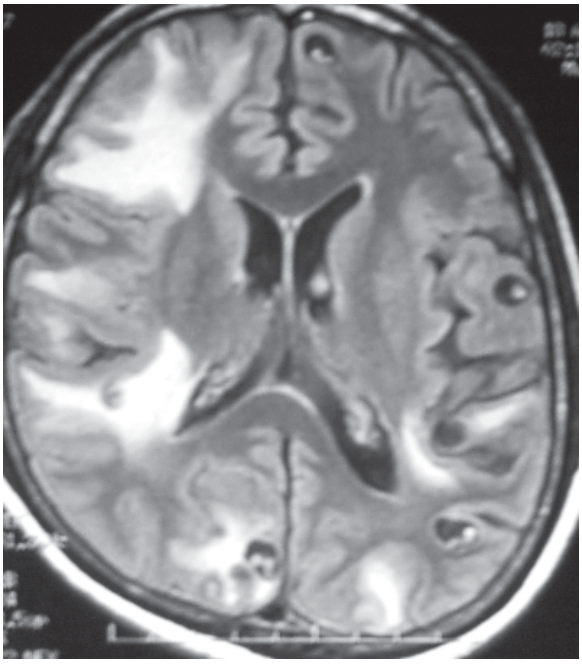

Fig. 2: MR imaging showing multiple viable cysts with perifocal edema. Lesions are also showing eccentric scolices

CSF in both T1 and T2-weighted images. However, MR imaging has been shown to have some superiority over CT as it may reveal many cysticerci that CT has missed. It has been observed that MR imaging is approximately four times more sensitive than CT in the detection of cysts (85% versus 21%) in the brainstem, in a subependymal location, in the cerebellum, in the subarachnoid space, intramedullary spinal cord and inside the ventricles. Calcified lesions are better seen with CT[4-9,11].

Serological Tests

Currently, the most sensitive and specific diagnostic test is an enzyme-linked immunoelectrotransfer blot assay (EITB). EITB assay with purified glycoprotein antigen (Western blot), which can be used both in serum and CSF samples. EITB has sensitivity of 98% and specificity of 100%. An advantage of EITB is that its sensitivity in serum is equal to or better than that in CSF. Major drawback is frequent false negativity in patients with single lesion in whom fewer than 50% tests are positive. The sensitivity and specificity of this test is also low calcified lesions. Standard enzyme-linked immunosorbent assay (ELISA) has disappointing sensitivity and specificity. CSF ELISA is 69% sensitive and 71% specific. Dot-ELISA is a simple and rapid test for the detection of cysticercus antibodies[4-9, 11,12].

Other Tests

Cysticercosis can be demonstrated on histopathological examination of subcutaneous nodules or on plain

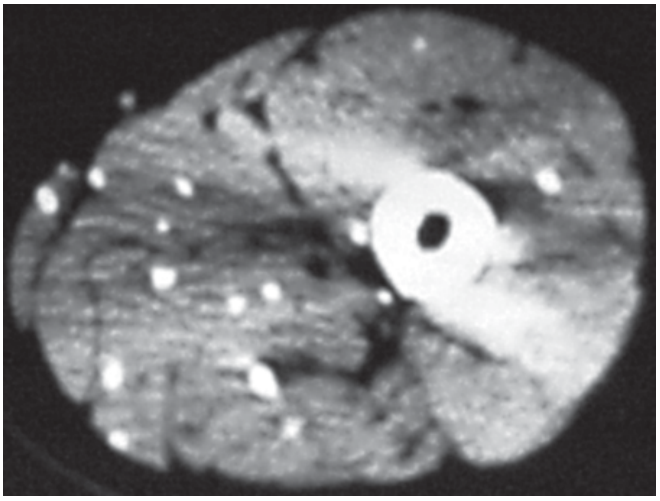

Fig. 3: CT of thigh showing multiple calcified cysticercal lesions

X-rays showing multiple "cigar-shaped calcifications in the arm, thigh and calf muscles (Fig. 3). Cysticercosis larva can be visualized 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.

Differential Diagnosis and Diagnostic Criteria

The differential diagnosis of neurocysticercosis depends on the type of clinical presentation. If cysts are

identified on CT or MRI scan, major diagnoses to be considered include tuberculoma, brain abscess, syphilitic lesions, arteriovenous malformation, metastatic tumor, small primary tumor, or another parasitic cysts. Tuberculomas tend to be larger than 20 mm in diameter, have an irregular outline, cause more mass effect, and have a progressive focal neurologic deficit, whereas C cellulosae cysts tend to be less than 20 mm in diameter, have smooth regular outline, and seldom cause progressive focal neurologic deficits. If the patient presents with a subacute or chronic meningitis or obstructive hydrocephalus, tuberculous meningitis, fungal meningitis, cerebrovascular syphilis, neurosarcoidosis, meningeal carcinomatosis, and CNS vasculitis need to be considered.

Del Brutto, et al, in 2001 published international diagnostic criteria for neurocysticercosis using a combination of clinical, radiological, serological and epidemiological factors. 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. 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. Keeping this in mind, modifications were suggested in the existing diagnostic criteria. In new criteria it was suggested that in certain situations diagnosis of neurocysticercosis should be made with caution. 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 (Tables 1 and 2)[13,14].

Table 1: Proposed diagnostic criteria for neurocysticercosis[13]

Absolute
Histological demonstration of the parasite
Cystic lesions showing the scolex
Direct visualization of sub-retinal parasites
Major
Lesions highly suggestive of neurocysticercosis like cystic lesions without scolex, enhancing lesions, or parenchymal calcifications
Positive serum EITB
Resolution of intracranial cystic lesions after therapy
Spontaneous resolution of small single enhancing lesions
Minor
Lesions compatible with neurocysticercosis like hydrocephalus
Clinical manifestations suggestive of neurocysticercosis like seizures
Positive CSF ELISA
Cysticercosis outside the CNS
Epidemiological
Evidence of a household contact
Individuals coming from or living in an area where cysticercosis is endemic
Frequent travel to disease-endemic area

Definitive diagnosis: Presence of one absolute criterion; Presence of two major plus one minor and one epidemiological criterion. **Probable diagnosis**: Presence of one major plus two minor criteria; Presence of one major plus one minor and one epidemiological criteria; Presence of three minor plus one epidemiological criteria

Table 2: Revised diagnostic criteria for neurocysticercosis[14]

Absolute
Histological demonstration of the parasite
Multiple cystic lesions with or without scolex on CT or MRI
Major
Lesions highly suggestive of neurocysticercosis like cystic lesions without scolex, enhancing lesions, or parenchymal calcifications
Spontaneous resolution or eventual calcification of the lesion
Positive serum EITB assay for the detection of antibodies against the parasite
Minor
Presence of a characteristic clinical picture
Positive CSF ELISA
Cysticercosis outside the CNS
Aggravation of existing symptoms or appearance of a new symptom following anticysticercal therapy
Diagnosis with caution in the presence of certain conditions*
Old age
Patients with pre-existing systemic tuberculosis or malignancy
Presence of HIV infection
Grossly abnormal neurological examination

Definitive diagnosis: Presence of one absolute criteria; Presence of two major plus one minor

Probable diagnosis: Presence of one major plus two minor criteria; Presence; Presence of three minor

*If diagnosis is not based upon one absolute criteria the conditions under "Diagnosis with caution in the presence of certain conditions" should always be considered

Management

Treatment of neurocysticercosis includes combination of antiparasitic and symptomatic therapy and use of surgery in appropriate cases. Treatment modalities include: (1) anticysticercal drugs such as albendazole or praziquantel in patients with viable cysts; (2) corticosteroids or other agents to suppress or prevent the host's immune response; (3) anti-seizure medication(s) to treat or prevent recurrent seizures; and (4) surgical interventions. Whether there is faster radiological improvement and/or clinical benefit in the treatment of cysts showing signs of inflammation by MR imaging (enhancement and/or edema) is controversial. There

was a strong consensus that there is no role for antiparasitic drugs in patients with only calcified lesions. Studies suggest that patients with single enhancing lesions will do well regardless of anticysticercal therapy. Anticysticercal drugs are contraindicated in patients with cerebral edema (cysticercal encephalitis). Most experts strongly recommend anticysticercal therapy in patients with multiple subarachnoid cysticerci or giant cysticerci. In patients with ventricular cysticerci, endoscopic removal is needed. However, recent evidence suggests that placement of a ventricular shunt followed by antiparasitic therapy is an acceptable alternative[4-9,11,12].

Albendazole and praziquantel are approved treatment of neurocysticercosis. Albendazole is well-tolerated with minimal adverse effects that include dizziness, gastrointestinal distress, rashes, leukopenia, and elevated serum liver enzymes. The mechanism by which the cyst dies is incompletely understood but the drug seems to interfere with energy production in the parasite, in part by blocking the ability of the parasite to uptake glycogen in the gut and interfering with cyst wall metabolism. The dose of albendazole is usually 15 mg/kg per day divided into 2 doses for 8 to 30 days. Praziquantel is also well absorbed orally and undergoes extensive first passage hepatic metabolism with the metabolites being inactive. The drug is well-tolerated with few side effects that include gastrointestinal distress, dizziness, fever, headache, and occasionally a diminished sense of well-being. The mechanism of action of praziquantel is poorly understood but the drug appears to kill the scolex and protoscolex. The usual dose of praziquantel is 50 mg/kg per day divided into 3 doses for 15 days[4-9, 11, 12, 15-17].

There is no general understanding when or how to use corticosteroids to suppress natural or treatment-induced inflammation around cysts although their use when inflammation contributes or could be expected to cause undue morbidity or mortality is reasonable. When albendazole is used, the corticosteroids should be given simultaneously and continued until day 5 or longer if there is a large parasite burden or a severe reaction develops. Dexamethasone, 8 mg to 24 mg per day in 4 divided doses orally, intramuscularly, or intravenously or prednisone 1 mg/kg per day orally are usually given. When praziquantel is administered, the corticosteroids are often withheld for 1 to 2 days or longer if possible since steroids decrease serum praziquantel levels by 50%. If increased symptoms develop, steroids are then administered intramuscularly or intravenously for rapid effect and continued as long as necessary[15-17].

Antiepileptic drugs are given in patients with seizures or patients who may likely develop seizures. Surgical intervention is required to alleviate mass effect, remove some cysts causing obstruction of the ventricles, shunt placement for hydrocephalus, and sometimes for removal and/or decompression of large or critically located cysts before anticysticercal treatment.

Prognosis

Three major arguments against the use of antiparasitic therapy in neurocysticercosis have been raised: first, that there are immediate risks because of neurologic symptoms due to the acute inflammation that results from the death of the cysts; second, that the long-term prognosis of the underlying seizure disorder may worsen because of increased scarring due to the acute inflammation; and third, that treatment is unnecessary since most cysts die by themselves within a short period. In a recent controlled study, there was a significant reduction in the rate of seizures with generalization and a non-significant decrease in the rate of partial seizures during follow-up among the patients who received albendazole as compared with those who received placebo. Moreover, cysts in the brain resolved much faster after albendazole therapy than after placebo[18-20]. Patients with massive parasitic load and chronic meningitis may have poor prognosis. These patients, if untreated, may experience brain herniation and death.

SOLITARY CYSTICERCUS GRANULOMA

Single enhancing CT lesions are the commonest radiological abnormality in Indian patients with partial seizures (Fig. 4). Histopathological studies have proved that neurocysticercosis is the most frequent cause for these lesions. Acute inflammation around the cerebral lesions of cysticercosis manifests as acute seizure disorder. These cysticercal granulomas represent 'colloidal' and 'nodular-granular' stages of a parenchymal cysticercus cyst. In 8-12 weeks time, majority of these lesions spontaneously disappear, few may calcify. As albendazole therapy is of controversial value, these patients, possibly, need to be treated only with antiepileptic drugs. Associated seizure disorder is also benign in nature and remit in majority after the lesion has disappeared. Antiepileptic drug may be withdrawn after resolution of the lesion[21].

CONCLUSION

Neurocysticercosis is a major zoonotic larval cestode infection that has a worldwide distribution and is of

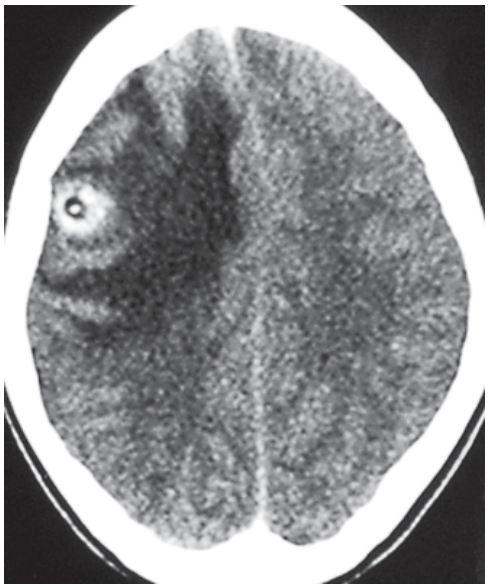

Fig. 4: CT image showing a solitary cysticercus granuloma with perifocal edema

significant public health importance. Improved sanitation, cooperation of veterinary and medical services, linkage with programs against epilepsy and cooperation of better educated communities are to effectively deal this gigantic problem.

REFERENCES

1. Flisser A, Sarti E, Lightowlers M, Schantz P. Neurocysticercosis: regional status, epidemiology, impact and control measures in the Americas. Acta Trop 2003;87(1):43-51.
2. Rajshekhar V, Joshi DD, Doanh NQ, van De N, Xiaonong Z. *Taenia solium* taeniosis/cysticercosis in Asia: epidemiology, impact and issues. Acta Trop 2003;87(1):53-60.
3. Wallin MT, Kurtzke JF. Neurocysticercosis in the United States: review of an important emerging infection. Neurology 2004;63(9):1559-64.
4. Garcia HH, Del Brutto OH. Cysticercosis Working Group in Peru. Neurocysticercosis: updated concepts about an old disease. Lancet Neurol 2005;4(10):653-61.
5. Del Brutto OH. Neurocysticercosis. Semin Neurol 2005;25(3): 243-51.
6. Carpio A. Neurocysticercosis: an update. Lancet Infect Dis 2002;2(12):751-62.
7. Alvarez JI, Londono DP, Alvarez AL, et al. Granuloma formation and parasite disintegration in porcine cysticercosis: comparison with human neurocysticercosis. J Comp Pathol 2002;127(2-3):186-93.
8. Alvarez JI, Colegial CH, Castano CA, et al. The human nervous tissue in proximity to granulomatous lesions induced by Taenia solium metacestodes displays an active response. J Neuroimmunol 2002;127(1-2):139-44.
9. Takayanagui OM, Odashima NS. Clinical aspects of neurocysticercosis. Parasitol Int 2006;55 Suppl:S111-5.
10. Ramirez-Bermudez J, Higuera J, Sosa AL, et al. Is dementia reversible in patients with neurocysticercosis? J Neurol Neurosurg Psychiatry 2005;76(8):1164-6.
11. Garcia HH, Del Brutto OH. Imaging findings in neurocysticercosis. Acta Trop 2003;87(1):71-8.
12. Dorny P, Brandt J, Zoli A, Geerts S. Immunodiagnostic tools for human and porcine cysticercosis. Acta Trop 2003;87(1):79-86.
13. Del Brutto OH, Rajshekhar V, White AC Jr, et al. Proposed diagnostic criteria for neurocysticercosis. Neurology 2001;57:177-83.
14. Garg RK. Diagnostic criteria for neurocysticercosis: some modifications are needed for Indian patients. Neurol India 2004;52(2):171-7.
15. Garg RK. Medical management of neurocysticercosis. Neurol India 2001;49:329-37.
16. Riley T, White AC Jr. Management of neurocysticercosis. CNS Drugs 2003;17(8):577-91.
17. Garcia HH, Evans CA, Nash TE, et al. Current consensus guidelines for treatment of neurocysticercosis. Clin Microbiol Rev 2002;15(4):747-56.
18. Carpio A, Hauser WA. Prognosis for seizure recurrence in patients with newly diagnosed neurocysticercosis. Neurology 2002:59(11):1730-4.
19. Garcia HH, Pretell EJ, Gilman RH, et al. A trial of antiparasitic treatment to reduce the rate of seizures due to cerebral cysticercosis. N Engl J Med 2004;350(3):249-58.
20. Del Brutto OH, Roos KL, Coffey CS, Garcia HH. Meta-analysis: Cysticidal drugs for neurocysticercosis: albendazole and praziquantel. Ann Intern Med 2006;145:43-51.
21. Garg RK. Single enhancing computerized tomography—detected lesion in immunocompetent patients. Neurosurg Focus 2002;12(6):e4.