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A Review: Neurocysticercosis Diagnosis and Treatment Issue

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ABSTRACT

Neurocysticercosis, the infection of central nervous system caused by the larval form of the tapeworm Taenia solium, is the most common parasitic disease of the central nervous system and the most common cause of acquired epilepsy worldwide .Neurocysticercosis (NCC) is infestation of human central nervous system with tissue cysts of pork tapeworm.Human beings acquire cysticercosis through faecaloral contamination or poor hygiene practices . Clinical presentation of NCC can be variable. This has primarily been a disease that remains endemic in southIndia(India).It is a disease of low-socioeconomic countries but increasing trend seen towards developed nations due to migration . Seizures are the commonest presentation of NCC [50-80%] (1,2). Various types of seizures have been described among patients with NCC including generalized, focal and rarely myoclonus and acquired epileptic aphasia. In general, it seems that about half the cases have partial seizures and the other half generalized seizures, a proportion similar to that of the general population (3-5). There are various issues related to management of NCC. The present article attempts to present the evidence and its critical interpretation to help in managing patients with NCC in routine practice and current literature on neurocysticercosis, including newer diagnostics and treatment developments i.e. newer imaging modalities and antilarvicidal measure.

Keywords: Neurocysticercosis, seizure, taeniasolium .

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DIAGNOSIS OF NEUROCYSTICERCOSIS (NCC):

Neuroimaging is the mainstay of diagnosis of NCC. Lesions suggestive of NCC on CT, in patients with compatible clinical picture in endemic areas are usually diagnosed as NCC(6). These criteria are very complex and need validation in population or hospital based studies. The major drawback of these criteria is that they do not help a clinician to differentiate NCC from tuberculoma. The access to Enzyme-linked immunoelectro-transfer blot assay (EITB) which is mentioned in the proposed criteria is limited in our country. The usefulness of these criteria has been questioned(7) CT is claimed to have sensitivity and specificity of over 95% for the diagnosis of NCC(8). The sensitivity of CT is much lower for ventricular or cisternal forms of the disease.MRI is the most accurate technique to assess the degree of infection, location and the evolutionary stage of the parasites. It visualizes well the perilesional edema and the degenerative changes of the parasite, as well as small cysts or those located in the ventricles, brainstem, cerebellum, base of the brain, eye and spine(9). CT is more sensitive for the detection of calcifications. The main disadvantages of MRI are its high cost and limited availability. Thus, in our setup, CT scan may be the first investigation and reserve MRI imaging for patients with inconclusive CT findings. Because of high incidence of small enhancing computerized tomographic lesion in our country, a CT scan is indicated after first focal seizure. After the availability of CT scans in India, patients with epilepsy were frequently found tomhave a lesion, which was termed as SSECTL. They are the commonest cause of partial seizures in children in India(10,11). After a long period of controversy, it is now believed that most of these lesions represent solitary cerebral cysticercus granuloma (SCCG). SCCG is the granular-nodular form of the parenchymal cyst. It accounts for nearly 60- 70% of all forms of NCC seen among Indian patients(12). The differential diagnosis could be tuberculoma, pyogenic brain abscesses, fungal abscess, toxoplasmosis, primary or metastatic brain tumor and infections vasculitis.

Single enhancing lesion on CT scan, and differentiation between NCC and tuberculoma:

Visualization of scolex by MRI or as eccentric dot on CT is characteristic of NCC. In patients in whom neuroimaging is not characteristic it may be difficult to differentiate between the two. In such cases diagnosis has to rely on associated features. Patients with a single enhancing lesion in the brain due to NCC are seronegative because the parasite is already dead or because a sole parasite does not elicit a strong antibody response and therefore, serology is not much of help. Many patients with tuberculoma do not have detectable tuberculosis in the lungs or in any other location to confirm the diagnosis. Rajshekhar, *et al.*(13) described CT criteria for differentiating NCC and tuberculoma. An enhancing ring lesion that is <20 mm in size, regular in outline and not producing a midline shift is likely to be NCC while with tuberculomas the lesion is usually >20 mm, irregular in outline and may produce midline shift. However the authors themselves believe that these criteria are not absolute and it may be difficult to differentiate a small tuberculoma from NCC by CT. MRI has better sensitivity to differentiate tuberculomas from NCC. Preliminary experience with Proton Magnetic Resonance Spectroscopy shows promise in differentiating tuberculoma from NCC(14).

The role of serology diagnosis of NCC:

The most commonly used ELISA is neither sensitive nor specific. It cross- reacts with other cestode infections like *Hymenolepis nana* and *Echinococcus granulosus*(15). ELISA has more sensitivity and specificity when done in CSF due to above reason. However, lumbar puncture should not be performed only for doing serological tests because of associated pain and invasiveness. The enzyme-linked immunoelectrotransfer blot assay (EITB) using purified extract of *T. solium* antigen was developed to detect the specific antibodies and was reported to have sensitivity of 98% and specificity of 100%(16). However, its sensitivity in case of single enhancing or calcified lesion is much lower(17). Serology should be used in conjunction with neuroimaging. Serology and neuroimaging evaluate different aspects of the disease and may disagree in some patients. Intestinal tapeworm carriers, naturally cured individuals or non-neurologic infections have normal brain imaging(18) but may be seropositive while individuals with only inactive lesion like calcification or those with a single cerebral lesion test seronegative(19). Antigen detection assays are also now available based on monoclonal antibodies, which perform well in comparison with other available tests on cerebrospinal fluid samples(20). There is limited evidence on sensitivity or specificity with serum samples. Thus currently available serological tests are of little value in clinical practice. However, serological tests are valuable for epidemiological studies.

Treatment option for NCC: The treatment modalities that can be offered to patients include

(i) larvicidal agents to kill the larvae;
(ii) corticosteroids to decrease or prevent inflammation;
(iii) Antiepileptic drugs to prevent or decrease the severity and number of seizures;
(iv) surgicalbased therapies including measures to remove the cyst and shunt placement for hydrocephalus.

A panel of experts analyzed the current consensus and disagreements in the management of neurocysticercosis (21). Their main conclusions were:

(i) therapeutic decisions should be adapted to the individual and should be based on the number, location and viability of the parasites within the nervous system;
(ii) growing cysticerci should be actively managed by either cysticidal drugs or surgical excision;
(iii) the management of intracranial hypertension secondary to NCC should take a high priority;
(iv) adequate management of seizures should be ensured.

Specially they agreed on the management of patients with moderate infections and viable cysts; calcified lesion; ventricular cysticercosis; subarachnoid cysts, including giant cysts or racemose cysticercosis and chronic meningitis; cysticercotic encephalitis . Patients with cysticercotic encephalitis should not be treated with cysticidal drugs because this may exacerbate the intracranial hypertension observed in this form of the disease. Patients with

granulomas and calcifications alone should not receive cysticidal drugs as these lesions represent dead parasites.There were disagreements about the use of cysticidal drugs in patients with only one or a few viable cysts, patients with massive infections with viable cysts, or patients with many degenerating cysts. In patients with both hydrocephalus and parenchymal brain cysts, cysticidal drugs may be used only after placement of a ventricular shunt to avoid further increases of the intracranial pressure as a result of drug therapy. But there are controversies regarding the use of cysticidal drugs for NCC, The main issue is whether cysticidal therapy or natural resolution of a cyst will lead to reduced scarring and thus improved prognosis in terms of epilepsy evolution. The Cochrane Database review on drugs for treating NCC concludes that there is insufficient evidence to assess whether cysticidal therapy in NCC is associated with beneficial effects(22).

Three major arguments against the use of cysticidal therapy in NCC have been raised:

(i) There are immediate risks because of neurologic symptoms due to the acute inflammation that results from the death of the cysts;
(ii) The long-term prognosis of the underlying seizure disorder may worsen because of increased scarring due to the acute inflammation(23)
(iii) Treatment may be unnecessary since most cysts die by themselves within a short period(24).

Contrary to above, in a recent double-blind, placebo-controlled study in patients with seizures due to viable parenchymal cysts, cysticidal therapy decreased the burden of parasites and was effective in reducing the number of seizures with generalization(25). Whether there is a clinical benefit from cysticidal treatment of patients with a single enhancing parenchymal cyst is controversial.

A few trials from India have assessed the effect of cysticidal therapy on SSECTL in adults and children(26-29). Better resolution on imaging and fewer seizures during follow up were reported in albendazole group in two of these trials(28,29). In contrast Gogia, *et al*.(30) did not show any benefit of albendazole in hastening resolution of CT lesions. While we discuss the arguments and counterarguments regarding cysticdial therapy, an additional, but commonly neglected, point to remember is that most patients feel highly uncomfortabl leaving a live parasite living in their brain(25). Thus though there is controversy about routine use of cysticidal drugs in single enhancing lesions, cysticidal drugs may be helpful in the management of some of these patients *e.g.*, persisting lesions as they hasten the resolution of the lesion, avoiding diagnostic pitfalls.

Praziquantel is an isoquinolone which produces spastic paralysis of the parasite musculature and destroys the scolex. It causes disappearance of 60-70% of parenchymal brain cysticerci after a 15 day course of treatment at a dosage of 50 mg/kg/day(31). Albendazole is an imidazole, which acts by inhibiting the uptake of glucose by parasitic membranes thus causing energy depletion. It was initially recommended to be administered at a dosage of 15 mg/kg/day for one month. Further studies showed that at similar dosages, length of the therapy could be

shortened to one week without lessening the efficacy of the drug(32). The optimal duration of cysticidal therapy for other less common forms such as giant cysts or subarachnoid forms is not known but should perhaps be longer than for parenchymal NCC(21). Albendazole destroys 75-90% of parenchymal brain cysts and has been superior to praziquantel in several trials comparing the cysticidal efficacy of these drugs(33). Other points favoring albendazole are its efficacy against meningeal, subarachnoid and ventricular cysticerci and its lower cost. Serum levels of praziquantel decrease when steroids are simultaneously administered, an effect that does not occur with albendazole. Whether it leads to lower cysticidal efficacy has never been demonstrated. Serum level of phenytoin and carbamazepine may also be lowered as the result of simultaneous praziquantel administration(34).

Corticosteroids and NCC:

Corticosteroids are used as an adjunct to cysticidal therapy to control the inflammatory reaction that usually occurs 2-5 days after initiation of therapy and decrease the symptoms (headache, nausea, vomiting and seizures) caused by the death of larvae. Its usage has not been standardized and is given empirically for a variable duration of 5-28 days(29,35). Oral prednisolone is preferred and should be started 2-3 days before cysticidal therapy and continued for 7-10 days along with cysticidal therapy since maximum exacerbation occurs during this period. All trials which have been done to evaluate cysticidal therapy have used steroids for a variable period of time. Whether steroids given alone in parenchymal NCC are beneficial is a matter of debate. Singhi, *et al.*(35) compared treatment with cortico-steroids or albendazole or both albendazole and steroids given for 28 days in a prospective trial of children with SSECTL. There was no significant difference in resolution of CT lesions in the three therapy groups at 3 and 6 months of follow-up, but children in the corticosteroid group had significantly more seizure recurrences while on antiepilepsy drugs. Contrary to this an open randomized trial in which patients either received antiepileptic drugs (AED) alone or AEDs with of short course of steroids (1 mg/kg of pred-nisolone for 10 days followed by tapering off over 4 days) showed that steroids help in rapid resolution of solitary cysticercus granuloma in patients with new-onset seizures(36). Thus, though corticosteroids are recommended to be used as adjunctive to cysticidal therapy there is conflicting evidence to support its use as the primary treatment in SSECTL. However, high dose corticosteroids are the primary therapy for cysticercotic encephalitis. In case of subarachnoid cyst, chronicmeningitic form or in case of multiple viable cysts steroids should be given along with cysticidal drugs.

Antiepileptic drug and schedule of antiepileptic drug therapy:

The antiepileptic drugs are no different in NCC than in other seizure disorder. Single first line antiepileptic drugs like phenytoin, carbamazepine result in adequate control of seizures. The optimal length of antiepileptic drug therapy in patients with NCC has been a subject of debate(37). The most rational way of defining the duration of antiepileptic therapy would be to characterize the seizures occurring with NCC. The seizures occurring with NCC may be either provoked or unprovoked according to the evolutionary stage of the cyst. Differentiating between provoked or acute symptomatic seizures and unprovoked seizures is vital in

determining treatment and prognosis. Patients with cysticerci in the degenerative phase develop acute symptomatic seizures because of the inflammatory response of the brain. Therefore these patients may be treated only for the duration of the acute condition, perhaps several months during which the inflammatory response is active. There are, however, no guidelines regarding the duration for which AED should be continued following an acute episode. In case of SCCG, it is most appropriate to monitor cyst activity with neuroimaging and to continue AED until resolution of the acute lesion. Most physicians repeat MRI or CT scan after 6 months in patients with parenchymal cysticercosis (earlier if the patient is symptomatic). Once the lesion has resolved on neuroimaging, antiepileptic drug may be tapered off over next 12 weeks. On the other hand, a patient with seizures who has inactive or calcified parasites may be categorized as having unprovoked seizures. The treatment in this case should last 2 years seizure free period. Treatment in patients with multiple lesions or extraparenchymal NCC has to be tailored according to individual case .The prognosis of epilepsy depends on multiple factors related to degree of infection and host response to parasite. Nearly, 85% of patients with a SCCG have a good seizure outcome following resolution of the lesion and early withdrawal of AEDs(38). Patients with more than two seizures, those with breakthrough seizures, and those whose follow-up CT scan shows a calcific residue of the granuloma have a higher risk of recurrence and therefore need to be appropriately cautioned after withdrawal of AEDs. The prognosis of epilepsy in patients with multiple cysts and residual calcifications is not as benign(39). The outcome of patients with multiple brain cysts and extraparenchymal NCC depend upon the location and severity of infestation.

There is increasing evidence indicating that calcific cysticercosis is not always clinically inactive and perilesional edema may at times be present around, apparently calcified foci(40). Perilesional gliosis demonstrated by magnetization transfer magnetic resonance Imaging was found to be predictive of need of long term anti-epileptic drugs(41). Besides epilepsy other sequelae include hydrocephalus, motor deficits and cognitive problems.

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