Neurocysticercosis - a review

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Cysticercosis is considered the most common parasitic disease of the central nervous system. It is caused by the larval stage of the tapeworm Taenia solium. The first observations on cysticercosis in humans were made in 1558 by Rumler in the brain of an epileptic person and in 1652 by Paranoli, who found some liquid-filled vesicles in the corpus callosum of an epileptic priest who died after a stroke, yet they did not identify the lesions as parasites. The correct nature of the disease was identified by Malpighi and Laennec in the 17th century. The word cysticercus is derived from Greek kystis= cyst and kerkos= tail because of their appearance. Today, massive immigration from endemic to nonendemic areas has produced a significant increase of cysticercosis in some countries where in past decades this disease was regarded as a medical curiosity.

Epidemiology
Cysticercosis remains as a major public health problem in developing regions of the world. The disease has a worldwide distribution. However, its prevalence is highly variable, depending mainly on sociocultural and economic factors. In some regions, it still presents a serious health problem with prevalence that may reach around 4% in general population. The true incidence of neurocysticercosis is difficult to assess. In Mexico, neurocysticercosis comprised 3% of all autopsies.

There are two main routes from which humans acquire cysticercosis: ingestion of food contaminated with human faeces containing T. Solium eggs and anus to mouth self contamination in patients harboring the adult worm in their digestive tract.

Parasitology
T. solium has complex life cycle involving two hosts human and pork. In the usual cycle of transmission, human acts as a definitive host where sexually mature stage of the cystode develops. Intestinal taeniasis is acquired by ingestion of the raw flesh of an intermediate host (pork). In the gut the larva matures into an adult worm whose head attaches to the upper intestinal mucosa. The adult T. solium may live in the small intestine for many years. It has a globular rostellum with four suckers and a crown of hooks. The body is composed by hundreds of proglottids. Gravid proglottids, each containing around 80,000 viable eggs, are usually present in stools of taenia carriers. This explains the contamination of water, vegetation, and food of communities living in poor hygienic conditions and high frequency of infection of subjects in contact with taenia carriers. The life cycle of the cystode is completed when pork, the natural intermediate host, ingests T solium eggs, which develop in brain and muscle resulting in cysticercosis, the embryonic stage of the parasite. Like wise, humans can also act as an intermediate host after ingesting T. solium eggs; in this circumstance human cysticercosis develops. The latter is a blind alley in the life cycle of T solium because it does not contribute to the reproductive success of the cystode.

Once in human stomach, T. solium eggs lose their coat by action of gastric juice liberating oncospheres (hexacanth embryos), which in turn cross the intestinal wall and enter the bloodstream to be carried to the tissues of the host where, after a period of 2 months, the larvae evolve forming cysticercus. Several organs of the body may be infected. However, the most frequently affected are the eye, skeletal muscle and central nervous system. In the latter parasites may lodge in brain parenchyma, subarachnoid space, ventricular system or spinal cord. The incubation period is uncertain.

Pathogenesis; Natural Course
Cysticercus is a fluid filled sac which varies in size from 0.5 to 5 cm or more in diameter. It has got a wall composed of three layers; innermost is reticular layer, middle one is cellular layer and outermost is cuticular layer.

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Scolex is a structure which resembles adult T solium and found in invaginated form inside the cysticercus sac. Scolex can be easily identified in biopsy or necropsy material by placing the vesicles (sac) between two glass slides and compressing firmly until the scolex flattens.

Cysticercus racemose (from lat. Racemus= clusters) is a cysticercus sac devoid of scolex. The racemose cysticercus is composed of giant cysts (>3cm in diameter) or by several large cysts attached to each other. It is most often seen in basal meninges.12

**Localization of parasites in the central nervous system**

1. Parenchymal
   - (a) Brain
   - (b) Spinal cord
   - (c) Eye

2. Extraparenchymal
   - (a) Ventricular
   - (b) Subarachnoid

Brain parenchymal cysticerci are usually small cysts, single or multiple, that tend to lodge in areas of high vascular supply.

Spinal cysticerci can be found inside the leptomeningeal space or intramedullary; both are locations, but former are more frequent than the latter.51 In general, morphologic features of spinal cysticerci are similar to those located within the brain, yet meningeal inflammation and fibrosis are usually more severe.12

Intraventricular cysts are usually single and tend to lodge in the fourth ventricle.13 In these cases the cysticercus reaches the ventricular system through the choroid plexus of the lateral ventricles and follows the CSF circulation. It seems that when the parasites arrive to the fourth ventricle, it has achieved a size large enough to prevent its passage to the subarachnoid space12; this mechanism would explain the preferential location of intraventricular cysticerci in the fourth ventricle.

Subarachnoid cysticerci may be small or large or may form large clumps of cysts within the subarachnoid cisterns. Presence of endarteritis in small arterial branches is common finding in meningeal cysticercosis.

**Immune Response of the Host**

Pericysticercal inflammation is composed mainly of lymphocytes, plasma cells, and eosinophils. This inflammatory reaction is protective in the sense that it leads to destruction of parasite and transformation into a calcified nodule. The degree of inflammation depends on degree of the immune response to cysticerci infestation. The spectrum of inflammation varies from intense immune reaction and immune tolerance.14 Correa et al15 studied the presence of Human Lymphocyte Antigen (HLA) – related antigens on the surface of cysticerci and found a direct relation between microscopic signs of damage to cysticerci and presence of HLA attached to their surface. Del Brutto OH et al16 documented that major histocompatibility complex restriction mechanisms are involved in the induction of cellular immune response against cysticercal antigens. Del Brutto OH et al17 also found that intensity of the host’s inflammatory reaction to parenchymal brain cysticerci is more severe in females.

**Clinical manifestations**

Cysticercosis affects men and women equally from birth to senility. The peak incidence is between the third and fourth decades of life.6 The clinical manifestations depend upon number and topography of lesions, the individual immune response to the parasite, and the sequelae of previous infestations.1,6,18-21

1. **Parenchymal NCC:- Common manifestations** are

   - Partial with secondary generalization
   - Other types

   I. Epilepsy
   II. Pyramidal tract signs
   III. Sensory deficit
   IV. Involuntary movements
   V. Cerebellar ataxia
   VI. Signs of brainstem dysfunction
   VII. Intellectual deterioration
   VIII. Dementia and psychosis
   IX. Cysticercotic

encephalitis/meningitis:- These patients present with signs and symptoms of increased intracranial pressure associated with mental disturbances, diminution of visual acuity, and generalized seizure.22,23

2. **Subarachnoid NCC**

   Manifests as headache, vomiting vertigo, cranial nerve dysfunction, gait disturbances, and mental deterioration due to hydrocephalus caused by widespread inflammation of subarachnoid
membranes and obstruction of the mechanisms of CSF absorption.\textsuperscript{24,25} Infarction of brain parenchyma is another complication of subarachnoid NCC.\textsuperscript{6}

3. Intraventricular NCC
The most frequent presentation is a subacute or intermittent syndrome of intracranial hypertension. Sudden death with acute hydrocephalus has been seen in some cases.\textsuperscript{26} Bruns’ syndrome is transient episodes of loss of consciousness due to cysts in the fourth ventricle. It is due to sudden interruption of CSF flow related to movement of the head.

4. Spinal NCC
Presentations are non-specific. Root pain, progressive weakness of insidious onset are features of leptomeningeal NCC. Intramedullary spinal NCC is found more often in thoracic segments of the spinal cord.

5. Ocular NCC
This is associated with progressive decrease of visual acuity due to presence of parasite in the eye or to an acute inflammatory reaction that causes vitritis, uveitis, or endoophthalmitis.\textsuperscript{27}

Pseudohypertrophic myopathy\textsuperscript{28} is a rare presentation of striated muscle cysticercosis.

Diagnosis
There are 3 clinical stages of NCC given by Sotelo & Carpio namely active, transitional and inactive NCC. Escobar defined 4 pathological stages of NCC. They are

1. Vesicular
2. Colloidal vesicular
3. Granular nodular
4. Nodular calcified

Vesicular is active form, colloidal vesicular and granular nodular represent transitional stage while nodular calcified stage is inactive stage of NCC.

Del Bruto et al has given diagnostic criterias for NCC. They are followings

1. Absolute criteria
   a. Histological proof
   b. Fundoscopic evidence
   c. Imaging (visualization of cysts with scolex)

2. Major criteria
   a. Imaging suggestive of NCC
   b. Immunological test
   c. Plain x ray revealing soft tissue shadow

3. Minor criteria
   a. Subcutaneous nodule
   b. Intracranial calcification
   c. Clinical manifestations
   d. Response to cysticidal drug (lesions go away)

4. Epidemiological criteria
   a. Patient belonging to an endemic area
   b. Frequent travel to an endemic area
   c. House – hold contact with taenia solium.

Degrees of certainty can be classified into definitive, probable and possible by combination of one or more of above criterias (Del Bruto 1996)

A. Definitive
   i. One absolute criteria
   j. Two major criteria
   k. One major + Two minor + One Epidemiological criteria

B. Probable
   i. One major + Two minor
   ii. One major + One minor + one epidemiological criteria
   iii. Three minor + One epidemiological criteria

C. Possible
   i. One major criteria
   ii. Two minor
   iii. One minor + One epidemiological

Diagnostic Techniques

Neuroimaging
CT head is still most useful diagnostic tool for the diagnosis of NCC.\textsuperscript{1,18} CT provides reliable information about the topography of the lesions and disease activity. There are four CT patterns of parenchymal NCC.

1. Small calcifications or granulomas
2. Rounded areas of low density showing little or no enhancement after intravenous contrast (vesicular cysts)
3. Scattered hypodense or isodense lesions surrounded by oedema and ring like
enhancement after contrast (colloidal cysts). These lesions represent the acute encephalitis phase of parenchymal NCC.29

4. Diffuse brain oedema associated with narrowing of lateral ventricles and multiple ring like areas of abnormal contrast enhancement in the parenchyma, (this is the CT appearance of cysticercotic encephalitis.22

CT findings of subarachnoid NCC
1. Communicating hydrocephalus
2. Abnormal enhancement of tentorium and basal cisterns due to fibrous arachnoiditis
3. Hypodense lesions in the sylvian fissure, cerebellopontine angle cisterns, or over the convexity of the cerebral hemispheres representing racemose cysticerci
4. Brain infarcts due to cysticercotic endarteritis.
5. Hypodense lesions in the sella region that usually represent a single giant cyst bulging up the diaphragm sella and extending to suprasellar cistern.30

Intraventricular cysticerci appear in CT as rounded areas of low density that deform the ventricular system and interfere with CSF circulation causing obstructive hydrocephalus.13

MRI:-
This method provides useful information in the evaluation of NCC patients, especially when CT findings are not conclusive.31,32,33 MRI permits precise characterization of NCC in terms of disease activity and its location. These advantages have important therapeutic implications.34

Benefits of MRI over CT in diagnosis of NCC are followings
1. Subarachnoid cysticerci are more readily identified with MRI than CT, particularly when they are located over the convexity of cerebral hemispheres or at the base of brain.
2. The scolex is visualized within the cyst as a high intensity nodule; this “hole-with-dot” imaging is characteristic of NCC.31
3. Adhesive arachnoiditis is visualized by MRI as a diffuse and heterogeneous increase in the signal intensity of CSF cisterns around the brainstem and cerebellum, especially after administration of gadolinium contrast.
4. Noninvasive diagnosis of intraventricular cysticerci is probably one of the best advantages of MRI.10

5. Conventional CT is insufficient for the diagnosis of intraventricular cysts and metrizamide CT ventriculography is frequently needed.35
6. Cysticerci within the spinal cord are easily detected by MRI.

Although some authors have considered MRI the best diagnostic method for patients with NCC32,36, CT scan is still of paramount importance. Both CT and MRI are mutually complementary in providing optimal non-invasive diagnosis.

Immunodiagnosis
All patients with suspected diagnosis of NCC should, undergo CSF examination. This provides reliable evidence of degree of inflammation and precise diagnosis by immunologic methods. Inflammation is manifested by elevation of proteins and cell count. When cell is inflammatory following immunologic tests can be done

1. ELISA:- Poor sensitivity and specificity
2. EITB:- (Enzyme linked immunoelectrotransfer blot) 100% sensitive, 98% specific.
3. Antigen specific IgM in CSF (87% sensitive 95% specific)
4. Complement Fixation

Immunoblot test has been used to confirm or exclude the diagnosis of NCC.37 But this test has not been evaluated in a large and unbiased group of neurologic patients and controls in whom the diagnosis of NCC has been definitively proved or ruled out by neuroimaging studies in all subjects, patients, and controls.39 Immunodiagnostic tests for testing serum has been disappointing due to a high proportion of false positives (about 30%) among healthy subjects from endemic areas.38,39,40

Treatment
A single therapeutic approach is not justifiable in NCC due to its pleomorphic nature that runs a particular course in almost every patient. The decisive factors for the treatment of NCC are activity of the disease and location of parasites. Two manistay of therapies are medical and surgical intervention.

A. Medical therapy (Cysticidal drugs)
   a. Albendazole (15mg/kg/day for 1 wk)
   b. Praziquantel (50mg/kg/day for 2 wk)

B. Surgical Therapy: indicated for intraventricular & subarachnoid NCC.

C. Antioedema measures (Steroids)
D. Antiepileptic drugs
Treatment of Brain Parenchymal Cysticercosis

General Principles are

i. Parenchymal granulomas or calcifications do not require treatment with cysticidal drugs because these lesions represent only the sequelae of previous cysts which were destroyed by the host’s immune system.

ii. Symptomatic treatment with antiepileptics is advised when calcifications are associated with seizure. In these cases, a trial with cysticidals is justified in those patients in whom there is a suspicion of active forms of NCC.

iii. Parenchymal cysts with little or no evidence of inflammation in imaging studies should be treated with a course of cysticidals.

iv. Patients with cysticerci in the acute encephalitic phase are also benefited from treatment with a cysticidal drug because these drugs are known to shorten the time to involution of lesions.

v. Patients with cysticercotic encephalitis must be admitted to the hospital for initial management with high doses of steroids. Follow up CT or MRI studies help decide on the use of cysticidal therapy in cases that show persistence of lesions.

<table>
<thead>
<tr>
<th></th>
<th>Albendazole</th>
<th>Praziquantel</th>
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<tbody>
<tr>
<td>Chemistry</td>
<td>1. Imidazole compound</td>
<td>1. Isoquinoline compound</td>
</tr>
<tr>
<td>Affordability and Quality</td>
<td>2. Cheap, intense cysticidal properties</td>
<td>2. Costly, effective against broad range of tapeworms</td>
</tr>
<tr>
<td>Status of Drug</td>
<td>3. Drug of choice for initial therapy of NCC</td>
<td>3. It may be initiated if there is partial response to albendazole</td>
</tr>
<tr>
<td>Duration of therapy</td>
<td>4. 1 week course is sufficient for active parenchymal NCC( )</td>
<td>4. 2 week course is required.</td>
</tr>
<tr>
<td>Interaction with steroid</td>
<td>5. ALB plasma levels increase with simultaneous dexamethasone administration.</td>
<td>5. Plasma levels are reduced by as much as 50% when dexamethasone is given simultaneously.</td>
</tr>
<tr>
<td>Superiority</td>
<td>6. Superior to PZQ</td>
<td>6. Inferior to ALB</td>
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Rational for use of cysticidals

Recent studies with long form clinical followup have shown that these drugs not only improve clinical manifestations of NCC, but also “cure” CT scans. There is reversal of neurologic deficits and better control of seizures.

Subarachnoid cysticercosis

Treatment for this form of NCC depends up on several factors. When arachnoiditidis complicated by secondary hydrocephalus, a ventricular shunt must always be placed before attempting other measures. When CSF analysis shows active disease, cysticidals are warranted following surgical procedure. A recent study demonstrated a better prognosis for patients with cysticercotic arachnoiditis managed with both ventricular shunt and PZQ when compared with patients managed with ventricular shunt alone. When active subarachnoid NCC is found in the absence of hydrocephalus, cysticidal treatment is also advised. Response to therapy should by guided by CSF findings before and after 3 months of therapeutic trial. The treatment of racemose cysticerci in the subarachnoid cisterns require ALB which induces the disappearance of cysts, obviating the need of surgery in many cases.

Ventricular Cysticercosis

The therapeutic approach to intraventricular cysticerci has been based on surgical extirpation due to low level of cysticidal drugs in the ventricular fluid. Nevertheless, some cases of successful drug therapy of ventricular cysts have been reported.

Spinal cysticercosis

Treatment for spinal forms of NCC disease activity. For active leptomeningeal NCC, a trial with anticysticercal drugs may be attempted.
Intramedullary spinal cysts are better removed at exploratory surgery.

**Ocular cysticercosis**

Until recently, the treatment of this worm of NCC was exclusively surgical. Unexpectedly, it has been shown that albendazole has strong cysticidal properties in ocular cysticercosis. Alter treatment with albendazole and dexamethasone, subretinal cysts are reduced to a small scar, whereas cysts in the vitreous cavity are killed and, once immobile, are easily extracted by surgery.50

**Prevention and Public Health Aspects**

The main measures for prevention of cysticercosis are:-

1. Proper disposal of human waste
2. Treatment of water contaminated with human feces before its use in irrigation of vegetable cultivation
3. Proper cooking of pork
4. Public education on life cycle of T. Solium
5. In endemic areas, measures such as compulsory and repeated treatment of taenia carriers and domestic or industrial freezing of pork.54
6. Production of vaccine against taenia solium.55

**References**

23. Lopez-Hernandez A, Garaizor C. Childhood cerebral cysticercosis: clinical features and

From the Internet

At the 1994 annual awards dinner given for Forensic Science, AAFS president Dr. Don Harper Mills astounded his audience with the legal complications of a bizarre death. Here is the story: On March 23, 1994, the medical examiner viewed the body of Ronald Opus and concluded that he died from a shotgun wound to the head. The decedent had jumped from the top of a ten-story building intending to commit suicide. He left a note to that effect indicating his despondency. As he fell past the ninth floor, his life was interrupted by a shotgun blast passing through a window, which killed him instantly. Neither the shooter nor the decedent was aware that a safety net had been installed just below at the eighth floor level to protect some building workers and that Ronald Opus would not have been able to complete his suicide the way he had planned. Ordinarily, Dr. Mills continued, "a person who sets out to commit suicide and ultimately succeeds, even though the mechanism might not be what he intended" is still defined as committing suicide. Mr. Opus was shot on the way to certain death nine stories below at street level, but his suicide attempt probably would not have been successful because of the safety net. This caused the medical examiner to feel that he had a homicide on his hands. The room on the ninth floor from whence the shotgun blast emanated was occupied by an elderly man and his wife. They were arguing vigorously, and he was threatening her with a shotgun. The man was so upset that when he pulled the trigger he completely missed his wife and the pellets went through the window striking Mr. Opus. When one intends to kill subject A, but kills subject B in the attempt, one is guilty of the murder of subject B. When confronted with the murder charge, the old man and his wife were both adamant. They both said they thought the shotgun was unloaded. The old man said it was his long standing habit to threaten his wife with the unloaded shotgun. He had no intention to murder her. Therefore the killing of Mr. Opus appeared to be an accident, that is, the gun had been accidentally loaded. The continuing investigation turned up a witness who saw the old couple's son loading the shotgun about six weeks prior to the fatal accident. It transpired that the old lady had cut off her son's financial support and the son, knowing the propensity of his father to use the shotgun threateningly, loaded the gun with the expectation that his father would shoot his mother. The case now becomes one of murder on the part of the son for the death of Ronald Opus.

➢ Now comes the exquisite twist. Further investigation revealed that the son was in fact Ronald Opus.
➢ He had become increasingly despondent over both the loss of his financial support and the failure of his attempt to engineer his mother's murder. This led him to jump off the ten-story building on March 23rd, only to be killed by a shotgun blast passing through the ninth-story window. The son had actually murdered himself, so the medical examiner closed the case as a suicide.