# Human cysticercosis and Indian scenario: a review

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Cysticercosis, caused by *Taenia solium* larva is a major public health problem, especially in the developing world and neurocysticercosis (NCC) is considered to be the most common parasitic infestation of the central nervous system. NCC is identified as the single most common cause of community acquired active epilepsy; 26.3% to 53.8% active epilepsy cases in the developing world including India and Latin America are due to NCC. It is also becoming more common in the developed world because of increased migration of people with the disease or *Taenia solium* carriers and frequent travel to the endemic countries. It is estimated that three quarters of the estimated 50 million people with active epilepsy live in the poor countries of the world. Recent Indian studies using neuroimaging techniques suggest that the disease burden in India surpasses many other developing countries. Hence it is important to know the epidemiology, pathogenesis and diagnostic criteria so as to assess the disease burden and adopt interventional strategies for its control. Literature search was done for this review with special emphasis on Indian studies to create awareness about the disease in India, since cysticercosis is preventable and potentially eradicable.

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## 1. Introduction

Cysticercosis caused by larval stage of the tapeworm *Taenia solium*, is a major public health problem, especially in the developing world. Neurocysticercosis (NCC) is considered to be the most common parasitic infestation of the central nervous system (CNS) and the single most common cause of epilepsy in the developing countries (Garcia *et al* 2003; Prasad *et al* 2008b). Three quarters of the estimated 50 million people with epilepsy live in the poor countries of the world and up to 94% of them remain untreated (Bertellote *et al* 1994). Human is the only definitive host of *T. solium* harbouring adult tapeworm in the intestine (taeniasis), where as both man and pig can act as intermediate hosts and harbour the larvae in different internal organs (cysticercosis) including brain (NCC). Human and pig both acquire cysticercosis through ingestion of eggs excreted in faeces by human *T. solium* carrier. *T. solium* infection is also increasingly diagnosed in affluent countries owing to human migration from endemic areas (Garcia *et al* 1996). Cysticercosis is common in communities where pigs are allowed to roam freely, the residents consume undercooked pork and the basic sanitary facilities are lacking (WHO 1983; Prasad *et al* 2007).

### 1.1 *Historical perspective*

Cysticercosis was first described in pigs by Aristophanes and Aristotle in 3rd century BC. Latter it was noticed in human by Parunoli in 1550. Cysticercosis has also been described in ancient Indian medical book, the *Charak Sanhita*. NCC was first reported in a coolie from Madras, who died due to seizure and was found to be infected with cyst on autopsy (Armstrong 1888). In 1912, Krishnaswamy (1912) reported cysticerci related case of muscle pains and subcuataneous nodules with abundant cysticerci in the muscles, heart and

**Keywords.** Active epilepsy; cysticercosis, neurocysticercosis; seizure; taeniasis; *Taenia solium*

Abbreviations used: AHDs, antihelminthic drugs; CNS, central nervous system; CFT, complement fixation tests; CSF, cerebrospinal fluid; EITB, enzyme electroimmune transfer blot; ELISA, enzyme linked immunosorbent assay; IHA, indirect haemagglutination tests; JE, Japanese encephalitis; LTT, lymphocyte transformation test; MRI, magnetic resonance imaging; NCC, neurocysticercosis

brain at autopsy. In 1934, high rate of new onset epilepsy related to cysticercosis in the British army deployed in India was noticed (MacArthur 1934).

### 1.2 *Epidemiology*

Cysticercosis has been designated as a "biological marker" of the social and economic development of a community (Carpio *et al* 1998; Sarti *et al* 1994). NCC is the single most common cause of seizures/epilepsy in the developing countries (Garcia *et al* 2003). It is difficult to exactly estimate the disease burden of NCC in a community study because (i) of polymorphic presentation of the disease as some patients suffer only one or two seizure(s) in the entire course of their illness while others get recurrent seizures, (ii) in some patients it remains silent throughout its infection (Fleury *et al* 2003) and (iii) some of the lesions might have disappeared or dissolved. Apart from these clinical features, social stigma associated with epilepsy prohibits the patients or their family member to come openly for medical assistance. On the other hand, some patients with other disorders (like patients with syncope, migraine with aura, somatoform disorders, transient ischemic attack, focal stroke, etc.) may present an acute event of seizure-like-symptoms. NCC is endemic in most developing countries of Asia, Latin America, Central and South Africa (Powell *et al* 1986). It is also being increasingly reported in the developed countries due to migration of persons with disease or *T. solium* carriers. Overall NCC is identified as the cause of active epilepsy in 26.3% to 53.8% in the developing world including Latin America (Del Brutto *et al* 2005; Montano *et al* 2005; Nicoletti *et al* 2005). The disease accounts for up to 2% of neurological and neurosurgical admissions in Southern California and more than 1000 cases per year in USA (Schantz *et al* 1996). Racemose/giant cysticerci, usually uncommon in immunocompetent hosts, had been reported in patients with acquired immunodeficiency syndrome (AIDS) (Delobel *et al* 2004). *T. crassiceps* cysticercosis, usually a rodent disease had also been reported in patients with AIDS (Francois *et al* 1998, Garg and Kar 2002). Cysticercosis is widespread among swine in Mexico and developing countries of Latin America (Flisser *et al* 1990b; Sarti *et al* 1994).

### 1.3 *Disease burden in India*

All the biological markers for transmission of *T. solium* taeniasis and cysticercosis exist in India. It is likely that the disease is under reported in India because due attention has not been given to this neglected disease and systematic population-based studies are lacking. There are great disparities within the country in geography, ethnicity, religion rituals, income, food habits, personal hygiene, level of education and standards of living, which are likely to influence the disease burden. Consequently there are wide variations in the frequency of cysticercosis in India (figure 1). There are only few reports from the State of Kerala, where the level of education and standards of hygiene are high, and from Jammu and Kashmir, a Muslim majority State due to prohibition of pork consumption by religion. Before the era of CT scan and magnetic resonance imaging (MRI), National Institute of Mental Health and Neuro Sciences (NIMHANS), Bangalore reported diagnosis of NCC in 2% of an unselected series of epileptics (Mani *et al* 1974). At a tertiary referral centre in New Delhi, NCC constituted 2.5% of all intracranial space occupying lesions (Wani *et al* 1981). With the availability of CT and MRI, the proportion of NCC in seizure disorders dramatically increased. Sawhney *et al* (1996) reported cerebral cysticercosis in 31% of patients in whom CT was done. In a community survey of 50,617 individuals from South India, the prevalence of active epilepsy was 3.83 per 1000 and NCC was detected in 28.4% of them by CT (Rajshekhar *et al* 2006). Cysticercosis appears to be more prevalent in the northern States Bihar, Uttar Pradesh through Punjab. In a recent study based on 30 cluster sampling approach suggested by WHO in the rural pig farming community of Mohanlalganj block, Lucknow district, Uttar Pradesh, the prevalence of taeniasis was 18.6%; factors associated with taeniasis were age above 15 years, history of passage of Taenia segment in stool, undercooked pork consumption and poor hand hygiene (Prasad *et al* 2007). In the same community active epilepsy was identified and clinically confirmed in 5.8% of the populations during door to door survey and 48.3% of them fulfilled either definitive or probable diagnostic criteria of NCC. Epilepsy in the family and no separate place for pig were identified as risk factors for NCC clustering (Prasad *et al* 2008b). The single cyst infection (range 47.7% to 53.4%), is the most common in Indian subcontinent (Prasad *et al* 2008a; Prabhakaran *et al* 2007). In a study of 156 histologically proven cases of cysticercosis from Patiala, Punjab, 88% patients presented with solitary lesion and the most frequent site being the upper arm, chest wall, eye, abdomen wall and neck (Saigal *et al* 1984). In a sero-prevalence study in and around Chandigarh, anti-cysticercus antibodies was found to be 17.3% with highest prevalence (24%) reported from slum areas; however only 8% of the sero-postives had previous history of seizure (Khurana *et al* 2006; Saigal *et al* 1984). Cysticercosis sero-prevalence among the healthy blood donors from Pondicherry was 6.5% using both antigen and antibody detection methods (Parija *et al* 2005). The prevalence of taeniasis ranged from 0.5-2% in hospitalized patients in northern India, 12–15% in labour colonies where pigs are raised (Mahajan *et al* 1982). The treatment gap in rural India is above 90% (Prasad *et*

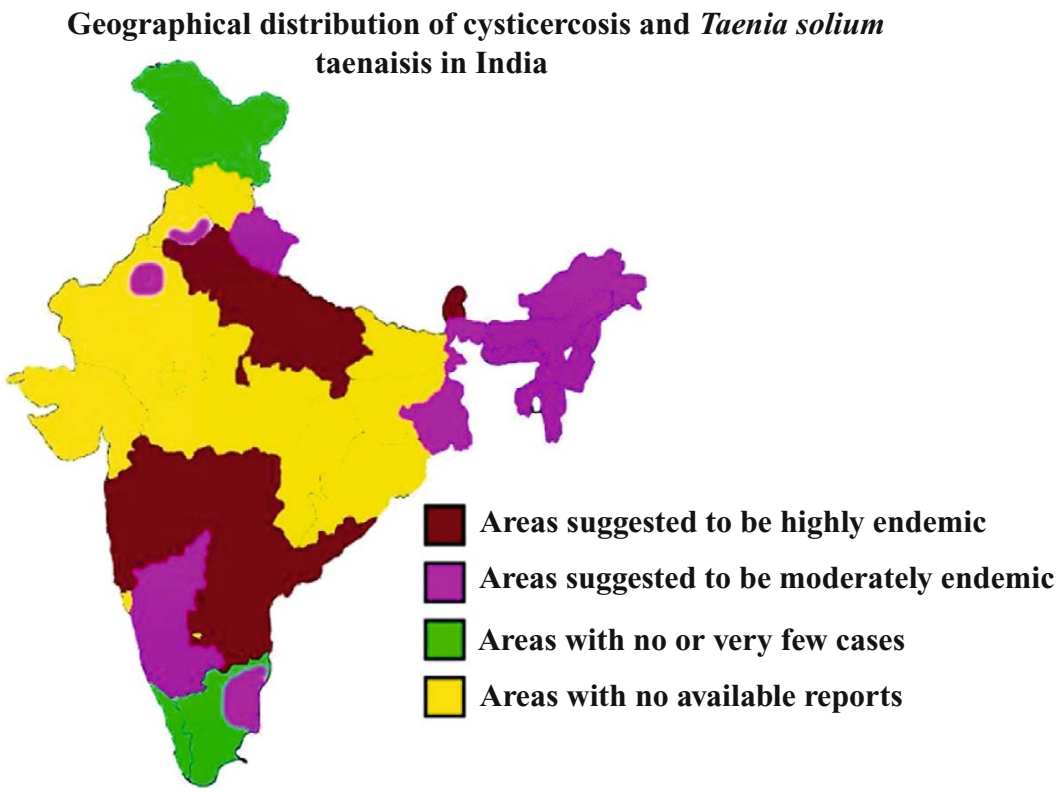


**Figure 1.** Geographical distribution of cysticercosis and *Taenia solium* taenaisis in India.

*al* 2008b) and the probable reasons for such high gap are socioeconomic, lack of knowledge and medical facilities, social prejudice to modern medicine and faith in alternative treatment modalities.

Cysticercosis also appears to be widespread among swine in India. In and around Chandigarh, 8–10% of the pigs slaughtered had cysticerci in their muscles and around 0.5% of the pigs reared in Government farms were found to be infected (Mahajan *et al* 1982). Another survey in slaughter houses of Kolkata (West Bengal) revealed cysticercosis in muscles of 7% of the slaughtered pigs (Ratnam *et al* 1983). Prasad *et al* (2002) reported a high frequency of cysticercosis (26%) in swine from Mohanlalganj block of Lucknow district in the State of Uttar Pradesh and 40% of them had cysticerci in the brain.

## 2. Life cycle, biology, and transmission

Life cycle of *T. solium* comprises two natural hosts, humans as the definite and swine as the intermediate host. Human harbours the adult tapeworm; eggs produced by the worm are disseminated to the environment through faeces. The pig ingests some of these eggs, which develop into cysticerci in internal organs like muscle and brain. When human consumes contaminated pork containing cysticerci, they develop into an adult worm in the small intestine (figure 2). The adult worm attaches itself to the intestinal mucosa by scolex equipped with four lateral suckers and a rostellum, which bears 25-50 hooklets. *T. solium* is a hermaphrodite and the gravid proglottides, containing the eggs reach the environment by passive discharge in the faeces. The eggs are spherical and measure 30-40 μm in diameter. After being liberated from the proglottides, the eggs can be ingested by swine and man. Once in the digestive tract, the eggs lose their coat by gastric and pancreatic enzymes and liberate hexacanth embryos or oncospheres. Aided by their hooklets, the oncospheres cross the intestinal wall and local venules, enter systemic circulation and are carried to different organs of the host (skeletal muscles, CNS, subcutaneous tissue, eye, etc.). Here the oncospheres lose their hooklets, acquire a vesicular shape and evolve into cysticerci by gradual evagination of the protoscolex (invaginated scolex) over a period of two months (Escobar and Neito 1972). The life cycle is completed when undercooked pork infested with cysticerci is eaten by human beings. However, man may also become an intermediate host and develop the larval stage of the disease in one of the ways: (i) by heteroinfection, the most common route, in which eggs present in food contaminated by the faeces of *Taenia* carriers are ingested; (ii) by exogenous autoinfection, due to ano-oral contamination in patients harbouring the adult worm; (iii) by endogenous

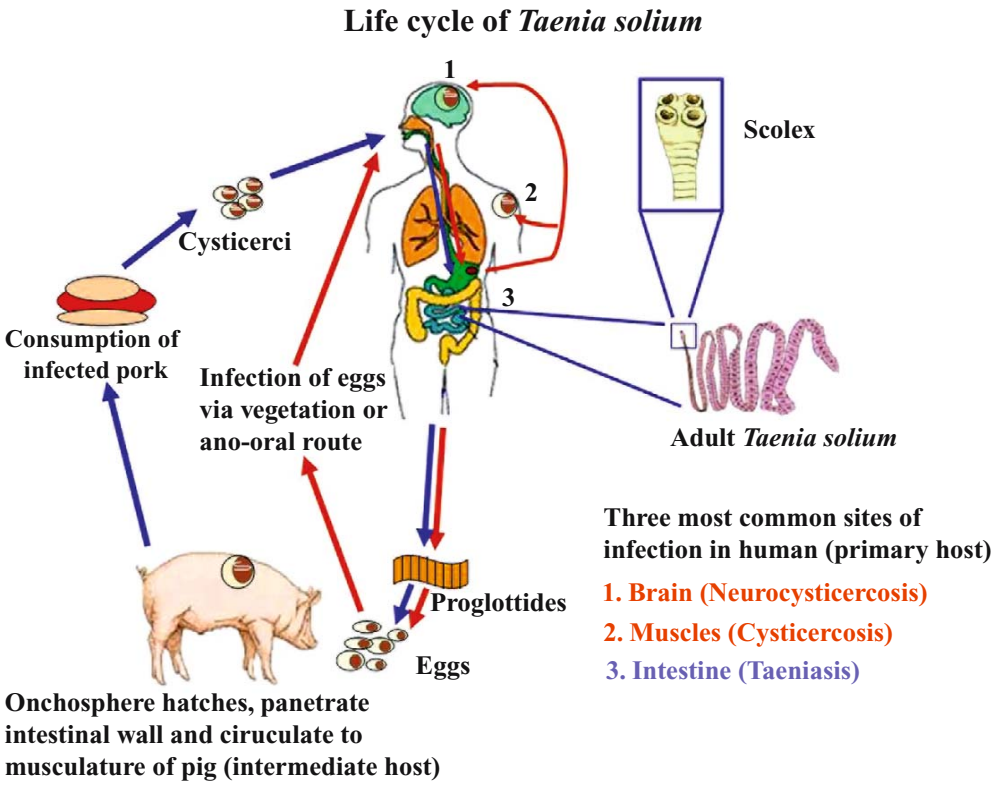


**Figure 2.** Life cycle of *Taenia solium.*

autoinfection, in which the eggs of the adult tapeworm living in the small intestine return to the stomach due to reverse peristalsis. The last two modes of autoinfection are far less frequent as it is quite uncommon to find patients having simultaneous infestation with cysticercosis and taeniasis in more than 10-15% cases (Rabiela-Cervantes *et al* 1982). In humans, parasite may get lodged in the CNS and results in NCC (Del Brutto and Satelo 1988). The larval stage also infests other tissues like skeletal muscle, diaphragm, heart and peritoneum, pleura and subcutaneous tissue (Shankar *et al* 1994). Mammals other than swine have also been reported to harbour cysticerci of *T. solium*. In Indonesia, examination of two sero-positive dogs revealed cysticerci of *T. solium* in their brain and heart (Ito *et al* 2002). *C. cellulosae* have also been recovered from the brain of a cat (Schwan *et al* 2002).

## 3. Clinical spectrum

Clinical spectra of the disease depend upon the localization of the cyst. NCC (cyst lodged in the CNS) is the most common form reported in literature with the brain parenchyma being the commonest site, followed by meninges, ventricles, eye and spinal cord. The manifestations of NCC are polymorphic; no symptom or sign is specific. Acute symptomatic seizures are the most common manifestation of human NCC; the other clinical conditions include headache, hydrocephalus, chronic meningitis, focal neurological deficits, psychological disorders, dementia, ocular and spinal cysts (Chandramukhi and Nayak 1990; Del Brutto 1996; Carpio *et al* 1998; David and Mathai 2000). In patients with extraparenchymal NCC the most common clinical symptoms and signs is hydrocephalus. The clinical presentation also varies with the stages and number of cyst. Sometimes NCC remains in the brain without causing any apparent symptoms; this form is called as asymptomatic NCC (Montano *et al* 2005; Prasad *et al* 2008a). Studies had suggested that NCC might influence the poor outcome of certain human cancers particularly glioma and haematological malignancies, and viral infections like Japanese encephalitis (JE) by modulating the host immunity (Del Brutto *et al* 1997; Desai *et al* 1997; Herrera 2000). In a South Indian study from NIMHANS, Bangalore, the co-existing NCC emerged as an indicator of poor outcome in patients with JE (Desai *et al* 1997). However, retrospective data analysis on 10,350 patients who underwent MRI over a period of 12 years, NCC could not be identified as risk for other intracerbral pathology including glioma and JE (Azad *et al* 2003). HIV and NCC co-infection, also with unusual racemose/ giant cysticercal cysts have been reported (Garg and Kar 2002; Delobel *et al* 2004). It is hypothesized that the impaired cellular immunity in HIV infected individuals may allow uncontrolled parasitic growth involving multiple

organs (Mauad *et al* 1997). Few NCC cases have also been reported in organ transplant recipients (Gordillo-Paniagua *et al* 1987; Bara Valencia *et al* 2002).

Ophthalmic cysticercosis (intraocular) manifests symptoms like proptosis, diplopia, and loss of vision while extraocular cyst resembles slow growing tumour or nodule with focal inflammation. Cysts in muscles may manifest as muscular pain, weakness or pseudohypertrophy. Subcutaneous cysticercosis is frequently asymptomatic but may manifest as palpable nodules.

## 4. Different form of NCC

NCC is a chronic and slowly progressive disease. Morphologically, four stages of development and regression of the cysticercus in the CNS are recognized (Sharda *et al* 2002; Grag 2002; Garcia *et al* 2003). (i) Cystic or vesicular stage is viable and composed of well-defined, fluid-filled membrane, which contains scolex. (ii) Degenerating, colloid or granular stage corresponds to parasite necrosis and associated inflammatory process. It appears as eosinophilic structures in which components of the bladder and scolex are in various stages of disintegration and tissue around have multinuclear giant cells, foamy macrophages, and neutrophils. Edema and/or necrosis of the surrounding neural tissue may be present in some cases. (iii) In the nodular stage, fibrosis develops with time, progressively occupy the entire lesion. This stage can be macroscopically recognized as a nodule of smaller size than the bladder in the preceding stage. (iv) The fibrous nodule thus formed undergoes mineralization and subsequently calcification. This may result from partial dystrophic calcification of the necrotic larva or from the presence of cysticercal calcareous corpuscle.

The lesions in the brain and the consequent onset of symptoms in NCC are mainly determined by (i) the number of lesions (single or multiple cysticerci), (ii) the location of CNS lesions (subarachnoid, intracerebral, intraventricular, intramedullary), (iii) the type of cysticercus (*C. cellulosae*, *C. racemosus*), (iv) the stage of development and involution of the parasite (vesicular, necrotic, nodular, calcified) and (v) the intensity of the host immune/inflammatory response.

In a necropsy study on war victims and road traffic accident deaths from Lima, Peru had shown the presence of a large numbers of different stages of NCC, in otherwise asymptomatic individuals (Evans *et al* 1996). In another CT based study in Salama, Honduras majority (84%) of individuals with active or calcified NCC compatible lesions were asymptomatic (Sanchez *et al* 1999). Similarly other studies from Latin America had found cases of asymptomatic NCC in their healthy controls (Montano *et al* 2005; Cruz *et al* 1999). Recently we have reported alarmingly high incidence of asymptomatic NCC cases (29.0%) with different stages of cysts among the family members of symptomatic NCC patients from pig farming community (Prasad *et al* 2007). Interesting 5 (16.1%) NCC positive asymptomatic family members had colloidal/degenerative parasite with rim enhancement and 3 (9.7%) had calcified lesions with edema on post-contrast. What triggers seizure in some patients and why others with similar stage of the parasite (as seen on MRI) remain symptom free is not clearly understood?

## 5. Diagnosis of NCC

The diagnosis of NCC is impaired by its polymorphic clinical presentations. A definitive or probable diagnosis of NCC can be made on the basis of proposed clinical, radiological and epidemiological criteria (Del Brutto 2001; Garcia *et al* 2005). Definitive diagnosis of NCC is made by direct demonstration of the parasite in tissues or radiological demonstration of scolex in cystic lesions using neuroimaging modalities. However, some reservations had been expressed from India due to presence of large number of single small enhancing CT lesions (SSCTL) in India, that may be due to presence of fungal and tubercular granuloma (Garg 2002; Garg and Kar 2002).

### 5.1 *Serological techniques*

A wide range of serological tests have been used in diagnostic and epidemiological studies of cysticercosis. Unfortunately, most of the tests that use unfractionated antigens are associated with high rates of false-positive and false-negative results (Ramos-Kuri *et al* 1992). Mahajan and colleagues were first to establish serum based techniques [complement fixation tests (CFT) and indirect haemagglutination tests (IHA)] for the diagnosis of cysticercosis (Mahajan *et al* 1974, 1975, 1982). They found that the antigens prepared from cysticerci were more sensitive than the antigens from the adult worms. They also found the IHA test to be more sensitive and specific than the CFT. Malla *et al* (1992, 2005) had compared the efficacy of enzyme linked immunosorbent assay (ELISA) and IHA for the diagnosis of NCC. The IHA technique was found to be specific for the detection of antibodies in cerebrospinal fluid (CSF) samples while cross reactions were observed with ELISA. In another study from Pondichery, South India, the co-agglutination (Co-A) test was moderately sensitive and specific for the diagnosis of cysticercosis (Parija and Reddy 2006).

5.1.1 *ELISA*: Serum based ELISA is not considered as diagnostic adjunct for NCC, however it is very much in use due to simplicity of the techniques. Three antigenic fractions from cysticerci were earlier used: scolex, wall and cyst fluid. Antigens from scolex and wall showed maximal discriminatory power between sick and healthy individuals with specificity of 98% and a sensitivity of 62% (Fliser *et al*

1975). Later, Ito *et al* (1998) had shown that the cyst fluid gave less back ground reactivity. Prabhakaran *et al* (2004) recently developed ELISA using the lentin-lectin affinity purified cyst fluid antigen with reported sensitivity 80% and specificity 94% for solitary cysticercus granuloma (SCG).

5.1.2 *Enzyme electroimmune transfer blot:* The use of enzyme electroimmune transfer blot (EITB), commonly known as Western blot (WB), was first published in 1986 for NCC (Gottstein *et al* 1986). Subsequently lentil lectin purified seven glycoprotein (Gp) bands with molecular masses of 50, 39–42, 24, 21, 18, 14 and 13 kDa (the total fraction is called LL-Gp) were found to be specific for human cysticercosis (Tsang *et al* 1989). Later the sensitivity was found to be related to the number of cysticerci in the brain: 98% sensitivity with three or more cysticerci, while only 65% sensitivity with one or two parasites (Plancarte *et al* 1994, 1999; Wilson *et al* 1991). EITB assay is more likely to be positive in serum than CSF samples. This test is currently commercially available and is also included as a criterion for diagnosis of NCC (Del Brutto *et al* 2001).

### 5.2 *Taenia solium cyst fluid antigens based lymphocyte transformation test*

Recently a new diagnostic method based on the principle of lymphocyte transformation test (LTT) has been established (Prasad *et al* 2008c). The test in its first study has shown a very good result with sensitivity of 93.7% and specificity of 96.2% for the diagnosis of NCC. Even for the single cyst infection the sensitivity of the test was 87.5%, which was much higher compared to EITB or ELISA. The procedure in its present from can only be performed at reference laboratory as the radioactive thymidine ($^3$H-TdR) has been used to measure the cell proliferation; however the test has the potential to be modified to non-radioactive technique like bromodeoxyuridine-ELISA LTT that can be used in general laboratories.

### 5.3 *Neuroimaging techniques*

Neuroimaging modalities such as CT and MRI have greatly improved the accuracy in the diagnosis of NCC (Sharda *et al* 2002; Garcia *et al* 2003). The neuroradiologic findings depend on the type of cysticercus, stage of larval development and involution, and location and number of cysts. On neuroimaging, four stages of cyst formation have been described. Imaging findings in each case reflect underlying changes in the disease process and host response. Vesicular stage of the cyst is seen on CT as hypodense containing a hyperintense small scolex along with nonenhancing or mildly enhancing cyst wall. In the colloidal vesicular stage, larva begins to disintegrate and the host's inflammatory response causes a fibrous capsule to form the surrounding parenchymal edema. CT depicts this stage as ring enhancing cystic lesions with hyperintense fluid content and surrounding edema. In the granular nodular stage, cyst retracts and forms granulomatous nodule, which is revealed by as an enhancing nodule with mild surrounding edema. In the final calcified stage, the granulomatous lesion is shrunken and completely calcified. On CT the lesion appears as single or multiple calcified nodules. *C. racemosus* is characterized by large size with absence of scolex and a protean appearance varying from that of a large bladder delimited by a delicate wall and with few lobulations to that of a complex of unequally sized bladders arranged like a cluster of grapes. CT has been claimed to have higher sensitivity and specificity for the diagnosis of calcified NCC. The sensitivity of CT is lower for ventricular or cisternal forms of the disease. MRI is the state of the art imaging technology and has become the primary technique in the routine diagnosis of many diseases. MRI is considered the best neuro-imaging tool for the detection of degenerating and innocuous (viable) cysticerci, while CT is the best for calcified lesions (Garcia *et al* 2003). The added advantage of MRI is that it can differentiate the stages of the parasite, which CT fails to do. Moreover, MRI with gradient echo sequence phase imaging has been reported as good as CT for the detection of the scolex in cystic lesions and also the calcified stage of the parasite (Gupta *et al* 2001). Although MRI allows better detection of the active parasites but some calcified parasites may be missed, especially in absence of gradient echo sequence.

## 6. Immunology

Little is known about the immune response generated at different stages of parasite due to scarcity of infected tissue. Living parasites in most cases do not elicit inflammatory reactions while dead or dying parasites are frequently associated with the pronounced inflammation (White *et al* 1997). Recently in mice, it has been shown that the parasite releases its outer glycoprotein layers from tegument to be recognized by brain tissue, this differential release of parasite material is believed to be responsible for immunomodulatory effects of the parasite (Alvarez *et al* 2008). In an earlier report on limited samples, Shankar *et al* (1995) had identified the glycocalyx as most antigenic site of *C. cellulosae*. When parasite begins to involute, either naturally or after some anti-parasitic treatment, a surrounding granulomatus inflammatory response develops both in human and swine. Predominant components of this immune response include plasma cells, lymphocytes, eosinophils and macrophages (Robinson *et al* 1997). Broadly the immune response can be divided into humoral and cellular components, which are described below.

### 6.1 *Cellular immune response*

To understand the immune response and associated pathology in NCC, rat/mouse has been widely used. The study in mice model has shown the abundant inflammatory response appearing as early as 2 days of post infection. Early granulomas are predominantly associated with Th1 response with abundant neutrophils, macrophages, natural killer (NK) cells, $\gamma\delta$T cells, $\alpha\beta$ T cells and B cells; whereas late granulomas have mixed Th1 and Th2 (IL-4) response. Thus Th1 response appears to play an important role both in the disease pathogenesis and clearing of the parasites, while IL-4 is involved in the down regulation of the initial response (Vila and Kuhn 1996; Restrepo *et al* 1998; Astrid *et al* 1999). Study of dying brain granuloma of NCC patients had shown abundant plasma cells, B and T lymphocytes, macrophages and mast cells with predominant Th1 cytokine response (Correa *et al* 1985). The inflammatory response in human depends upon the evolutionary stage of the parasite, the intensity of inflammatory reaction decreases with successive stage of evolution i.e. most severe inflammation is found at colloidal stage while only scattered inflammatory cells are seen at calcified stage; however a dead cysticercus evokes a strong inflammatory reaction, having B and T lymphocytes, mast cells, eosinophils, macrophages, neutrophils, plasma cells in abundant (Robinson *et al* 1997; Luis *et al* 1998). Observation made in animal model is quite interesting, as it has shown the Th1 response when the parasite is intact and a mixture of Th1 and Th2 when the parasite destruction starts. This finding supports the belief that the parasite maintains equilibrium with host immune response in early infection, so a mild Th1 response with IgG is provoked, but as the time passes this equilibrium is disturbed towards Th2 response that leads to parasite destruction. The precise mechanism underlying the Th1 and Th2 immune response to natural and experimental cysticercosis is yet to be clarified (Del Brutto *et al* 2005).

### 6.2 *Humoral immune response*

Humoral response is better understood than the cellular one. Studies were done by infecting piglets with *T. solium* eggs. It was found that intense humoral response occurred 10-30 days of post infection which persisted up to 90 days (Grewal *et al* 2000). The humoral response in NCC is related to the magnitude of infection and is mainly an IgG response, which indicates a chronic infection. The humoral response is generally greater in patients with multiple cyst infections, compared to single cyst infection. Similarly antibody responses were found to be proportional to the intensity and duration of infection. Several immunoglobulin classes are produced as specific antibodies against the parasites i.e. IgG, IgM and little of IgE. The most frequent is IgG, and subtype IgG2b, IgG2a and IgG1 in serum, CSF and saliva, which suggests that the infection is of long duration (Corona *et al* 1986; Luis *et al* 1998). After the second week of infection there is a significant increase in IgG2a production, later this isotype is dramatically down regulated. Concomitantly the specific IgG2b, and IgG1 anti-cysticerci antibodies that are at low level in early infection increases as infection progresses but most prominently IgG1 isotype (Kaur *et al* 1995). Earlier studies had observed that the IgG antibody responses in pigs generally increased 6-8 weeks post infection (Cho *et al* 1988). Cysts obtained from brain, eye and muscles of patients have demonstrable host IgG, IgM, IgA, and IgE on their surface and surrounding fluid, suggesting that the living parasites mask themselves with host immunoglobulins, probably through Fc receptors on the surface of the teguments, which could play a role in endocytosis (Flisser *et al* 1990a). Thus humoral response to NCC is very heterogeneous; it is also evident from the fact that patient antibodies may react to 1-8 antigens on immunoelectrophoresis and upto 30 antigens on EITB (Pardini and Vaz 2001). On immunoelectrophoresis, CSF from NCC patients strongly reacted with the 80 kDa, 30 kDa, 18 kDa, 14 kDa fragments of cyst lysate (Cruz *et al* 2000), while on EITB the serum and CSF from these patients reacted with the GP-50, GP-42-39, GP-24, GP-21, GP-18, and GP-13 (Tsang *et al* 1989).

### 6.3 *Immune response against different antigens*

The viable cyst usually induces no or minimum immune response, however the dying cysticerci (when the outer wall starts degenerating) induces intense infiltrates that are associated with the pathology and granuloma formation; however suppressed response in NCC patients by mitogen, crude lysate, membrane extracts from scolex and vesicular fluid of *T. crassiceps* has also been reported (Chavarria *et al* 2006). Studies investigating the immune response generated by crude cyst lysate, cyst wall or cyst fluid alone in the same patient populations are lacking. Chavarria *et al* (2006) used whole *T. solium* crude antigen for lymphoproliferation in symptomatic and asymptomatic NCC cases and reported Th2 immune response (IL-4, IL-5, IL-13) in asymptomatic NCC cases.

## 7. Genetic factors

Most of the human disorders are a result of an interaction between environmental and genetic factors. Del Brutto *et al* (1991) reported significantly increased frequency of HLA- A28 and decreased frequency of HLA– DQW2 in a Mexican cohort with parenchymal NCC. In a study from North India, Jain *et al* (1997) had shown increased proportion of HLA- B63 and HLA– B58, while decreased HLA- A11 in patients with SSCTL; however the differences were not significant after the application of correction

factor. The role of different host genetic factors like toll-like receptors and certain pro and anti inflammatory cytokines associated with pathogenesis should be studied to determine the relation between occurrence and resistance to symptoms. The identification of genetic factors may help in determing the susceptible populations.

## 8. Animal models

Animal models are critical to understand the host-parasite relations, immuno-pathogenicity and other factors involved with the disease acquisition and development of novel therauputic agents. Several mammals have been evaluated as experimental models for *T. solium* infection. Models like young dogs, Rhesus monkey and cat were infected with cysticerci obtained from pigs by oral route but the tapeworm survived only 8–14 days in these models (Marvilla and Cabrera 1998). Golden hamster, Gerbil and Guineapigs had exhibited greater sexual development, although infectious oncospheres were not produced (Allan *et al* 1991).

Porcine cysticercosis is a successful experimental model for *T. solium* cysticercosis, as pigs are the natural intermediate host of the helminthes. Currently the understanding of immunopathogenesis is based on the mice or rat models, which can not be extrapolated to human being. Swine is the natural intermediate host of *T. solium* and it has been reported that the course of infection and its histopathology in swine is similar to human and the response shown by the swine against anti-parasitic treatment follows the same pattern as shown by human (Gonzalez *et al* 1990; Chawala *et al* 2004). In pigs the infection is apparently benign despite the presence of thousands of cysticerci throughout the body (Flisser *et al* 1990a). However, recently clinical signs like excessive salivation, excessive blinking and tearing, and subconjunctival nodule has been reported in swine with cysticercosis (Prasad *et al* 2006). Only a single centre study is available from India where swine was used as the experimental model for cysticercosis (Kaur *et al* 1995). In another report, while studying the kinetics of immune response, the authors observed that cellular response was triggered at late stage of the cyst when compared to humoral response (Grewal *et al* 2000). However, the limitation of these studies was that none of the experimentally infected swine had cysticerci in the brain.

## 9. Treatment of NCC

Treatment for NCC with antihelminthic drugs (AHDs) such as metriphonate, mebendazole, flubendazole, praziquantel and albendazole were published more than 15 years ago, but clinical trials to establish the specific indications, definite doses, and duration of treatment are lacking. Some authors suggest that control of seizures in patients with NCC is better after a course of anticysticercal drugs (Garcia *et al* 2004; Medina *et al* 1993) and that the chance of remaining seizure free after the withdrawal of anti-epileptic drugs (AEDs) seems to be greater in those patients who were previously treated with AHDs (Del Brutto *et al* 1996). Albendazole and praziquantel effectively destroy the cerebral parenchymal cystic lesions. Albendazole is possibly more effective in subarachnoidal, ventricular and spinal cysticercosis, and frequently obviates the need for surgery. Recently, there is an intense debate on usefulness and safety of anti-cysticercal treatment (Singh and Sander 2004). Opponents of anticysticercal therapy argue that effectiveness of therapy is possibly a reflection of natural course of the disease and even if cysticercal lesions are left untreated, they either disappear spontaneously or are calcified (Mitchell and Crawford 1988; Kramer *et al* 1989). Anticysticercal therapy may aggravate cerebral edema, produce vasculitis and stroke, which may even lead to death. To minimize these risks, concomitant corticosteroids is administered especially if there is a massive parasitic load. Anticysticercal treatment is avoided in patients with cysticercotic encephalitis (Del Brutto and Sotelo 1988; Carpio *et al* 1998). There was a strong consensus that there is no role for antiparasitic drugs in patients with only calcified lesions (Riley *et al* 2003). Most experts strongly recommend antiparasitic therapy in patients with multiple subarachnoid cysticerci or giant cysticerci.

## 10. Prevention and control

Cysticercosis has been recognized as a potentially eradicable disease. The main method of control in developed countries has been the eradication of swine cysticercosis through improved animal husbandry and meat inspection procedures. This approach has resulted in the successful interruption of transmission of intestinal *T. solium* in the United States and Western Europe (Ferreira *et al* 1997). A small number of individuals with tapeworm may infect vast numbers of healthy human beings. Tapeworm carriers are an appealing target for the control of cysticercosis/taeniasis. In the developing world, emphasis has been placed on control of the parasite through health education and mass administration of antihelminthic drugs in areas of endemicity in an attempt to remove tapeworm carriers (Plancarte *et al* 1999; Garcia *et al* 2003; Lightowlers 2003).

### 10.1 *Vaccination*

Till date no vaccine has been developed against the *T. solium* although many groups had reported the success of a few proteins in vaccination of porcine cysticercosis. However the complex immunology of the parasite, occult nature of this infection and the minimal morbidity associated with

this infection, make taeniasis a poor candidate for vaccine development. Vaccination against taeniasis does not, therefore, appear to be immunologically or logistically feasible at the present.

Vaccinating pigs in endemic region to prevent porcine cysticercosis may be good strategy to improve animal health, meat yield and to break the parasite life cycle, preventing taeniasis and consequently preventing human cysticercosis. In laboratory and field studies, a variety of antigens have demonstrated effective partial protection (Lightowlers 2003). A protective antigen from *Taenia ovis* oncosphere-stage has been cloned to develop a recombinant vaccine for ovine cysticercosis and this vaccine is available commercially for veterinary use in New Zealand (Rickard *et al* 1995). On the basis of evidence of a similar immune response to *T. solium*, it should also be possible to develop an effective vaccine to prevent both human and swine cysticercosis (Mitchell and Crawford 1997). It has been proposed to develop a safe, effective, inexpensive vaccine for swine, which can be administered in an edible form (Eddi *et al* 2003).

## 11. Conclusions

Cysticercosis is a global public-health problem, especially so in developing countries including India. It is considered as a "biological marker" of social and economic development. NCC is the most common parasitic infection of the CNS and identified as the most important cause of acquired active epilepsy. Systematic population-based studies are lacking in most parts of the country; hence it is difficult to estimate the disease burden in India. However, few recent studies using CT and MRI reveal that NCC is alarmingly high in India especially among the communities with low socioecomic status with treatment gap of more than 90%. Since cysticercosis is a preventable and eradicable disease, appropriate measures like health education, mass awareness, better medical facilities, mass treatment of *T. solium* carriers, and restriction on sale of measly pork may help to reduce the disease burden in the endemic areas.

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