Journal of Pharmacognosy and Phytochemistry

Available online at www.phytojournal.com

E-ISSN: 2278-4136
P-ISSN: 2349-8234
JPP 2018; 7(6): 303-312
Received: 01-09-2018
Accepted: 03-10-2018

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An overview on Neurocysticercosis

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Abstract
Neurocysticercosis is a parasitic disease caused by metacestodal stage of *Taenia solium*, and is one of the most common causes of epilepsy in man. The commonest manifestation of neurocysticercosis in humans is acute symptomatic seizures, which might be due to the degenerating cysts or calcified granulomas, and rarely due to infarcts in patients with subarachnoid involvement. As cysticercosis is a largely considered preventable and eradicable disease, appropriate corrective measures like health education to susceptible people, better medical facilities, mass awareness and treatment of *T. solium* carriers, and proper meat inspection and proper treatment of measly pork may help to reduce the disease burden considerably in the endemic areas. Cysticercosis is a serious public-health problem especially in resource poor and developing countries including India. It is considered as a biological marker of social and economic development. The present review was aimed to provide an update regarding the Neurocysticercosis in India and abroad.

Keywords: Neurocysticercosis, parasitic disease, metacestodal, *Taenia solium*

Introduction
Neurocysticercosis (NCC), a parasitic disease caused by metacestodal stage of *Taenia solium*, is the most common cause of the acquired disease (epilepsy) of nervous system in man (Garcia *et al*., 2003) [30]. Its prevalence varies greatly according to the geographical region and is not yet precisely known (Cameron *et al.*, 1997) [6]. NCC is one of the most important neglected tropical diseases. NCC is the single most common cause of epilepsy in most of South and Central America, India, Southeast Asia, China, and sub-Saharan Africa. Diagnosis and management of NCC is often difficult due to wide variation in the neuropathology and clinical symptoms. Besides widespread anthelmintic resistance, inability of anthelmintic drugs to prevent reinfection and relapse further complicates the disease scenario. Owing to its long incubation period, the disease is seldom seen in children younger than 7 years. It predominantly affects adults in their third or fourth decade of life; it is uncommon in children and elderly people (Carpio, 2002) [7]. Clinical presentation of NCC varies greatly from asymptomatic infection to sudden death depending on the number, size, stage and localization of cysts and the patient's immune response. It has been found that 50- 80% cases of NCC present as seizures (Del Brutto *et al*., 1992) [17]. Seizures can be generalized, focal and rarely myoclonus and acquired epileptic aphasia. Seizures can be either partial or generalised which account for half of the cases (Kalra *et al.*, 1992) [44]. Cysticerci can lodge in any tissue of the body, but Neurocysticercosis i.e. development of cysticerci central nervous system is the clinically most important manifestation of the disease in humans and may lead to epilepsy and death (Sorvillo *et al.*, 2007) [108].

Historical perspective
Ancient Egyptians were the first to describe tapeworms in 2000 BC (Wadia *et al.*, 2002) [115]. Ancient Greeks also knew about the tapeworms as described by Aristotle (384– 322 BC). Tapeworms were known to Jewish and Muslim physicians and may be the reason for pork being forbidden by Jewish and Islamic dietary laws (Oscar *et al.*, 1998) [69]. Cysticercosis in pigs was described by Aristophanes and Aristotle in 3rd century BC. First human case of cysticercosis was noticed by Parunoli in 1550. Rumler (1555) described cysticercosis; however relation between tapeworms and cysticercosis was elucidated by Küchenmeister, 1850 when he experimentally infected prisoners awaiting execution by feeding pork containing cysticerci and later recovered the developing and adult tapeworms from their intestines during autopsy. By the middle of the 19th century, it was clear that cysticercosis was caused by the ingestion of the eggs of *T. solium* (Küchenmeister *et al.*, 1861) [50]. Cysticercosis has been described in Charak Samhita, the ancient Indian medical book. First report of NCC was from a coolie from Madras, who died due to seizure and on autopsy revealed cyst

(Armstrong, 1888) [2]. Krishnaswamy (1912) [49] reported cysticerci related case of myalgia and nodules in subcutaneous tissues with abundant cysticerci in the muscles, heart and brain at autopsy. MacArthur (1934) [53] reported high rate of cysticercosis in the British army deployed in India suffering from epilepsy.

Life cycle, biology, and transmission

T. solium life cycle comprises two natural hosts. Man acts as the definite host harbouring the adult tapeworm in the intestine passing the eggs in faeces while pig is the intermediate host which ingests some of these eggs leading to development of cysticerci in internal organs like muscle and brain. Humans become infected by consuming pork contaminated with cysticerci. The scolex of adult worm is equipped with four lateral suckers and a rostellum is armed bearing 25-50 hooklets by which it attaches itself to the intestinal mucosa. The gravid proglottids containing the eggs are passively discharged in the faeces.

The shape of eggs is spherical and diameter ranges from 30-40 µm. Once proglottids are voided in faeces and eggs are liberated from the proglottids, these can be ingested by swine and man. After being ingested the eggs lose their coat and liberate hexacanth embryos or oncospheres under the influence of gastric and pancreatic enzymes. The oncospheres by the help of their hooklets, cross the intestinal wall and local venules, enter systemic circulation and are carried to different organs of the host such as skeletal muscles, CNS, subcutaneous tissue, eye etc. Oncospheres after reaching the organs lose their hooklets, acquire a vesicular shape and evolve into cysticerci by gradual evagination of the protoscolex. The process of development of cysticerci takes about two months (Escobar and Neito, 1972) [22]. Humans ingest the raw or undercooked meat contaminated with cysticerci and life cycle is completed. In NCC, humans act as an intermediate host in one of the ways: (i) When food contaminated by the faeces containing eggs of *Taenia* carriers is ingested (heteroinfection) - the most common route (ii) by ano-oral contamination in patients harbouring the adult worm (exogenous autoinfection) (iii) by reverse peristalsis by which the eggs of the adult tapeworm living in the small intestine return to the stomach (endogenous autoinfection). It is quite uncommon to find patients having simultaneous infestation with cysticercosis and taeniosis due to concomitant immunity in more than 10-15% cases (Rabiela-Cervantes *et al*. 1982) [87], hence the last two modes of infection are uncommon. The cysticerci may get lodged in the CNS In humans resulting in NCC (Del Brutto and Satelo 1988) [12]. Cysticerci also infest other tissues like diaphragm, skeletal muscle, heart and peritoneum, pleura and subcutaneous tissue (Shankar *et al.* 1994) [104]. Besides swine, other mammals have also been reported to harbour cysticerci of *T. solium*. In Indonesia, two sero-positive dogs on examination revealed cysticerci of *T. solium* in their brain and heart (Ito *et al.*, 2002) [42]. C. cellulosae have also been recovered from the brain of a cat (Schwan *et al.*, 2002) [103].

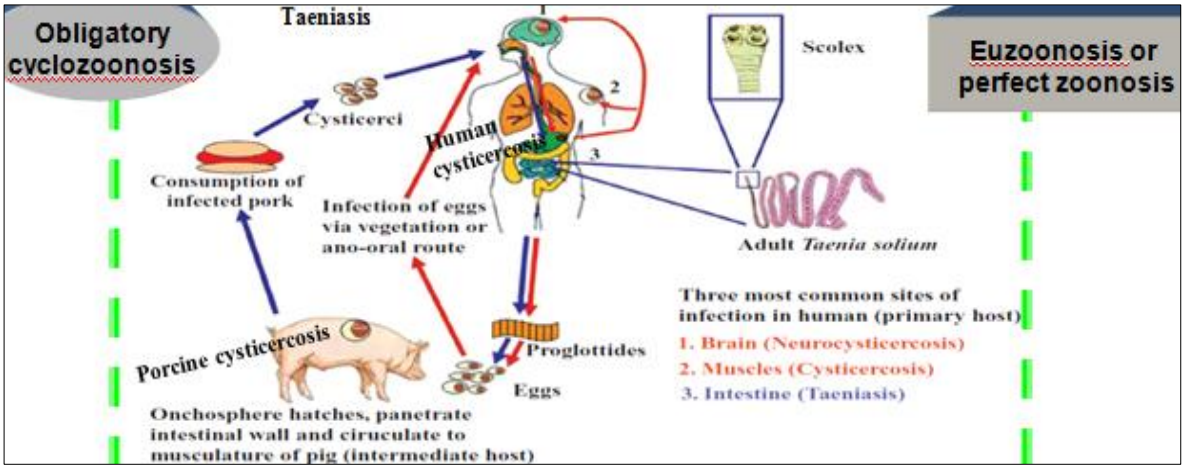

Fig 1: Life cycle of *Taenia solium*. (Adopted from Prasad *et al.*, 2008; Human cysticercosis and Indian scenario: a review)

Epidemiology and Geographical distribution

Disease burden in India in humans

Although all the favourable factors for transmission of *T. solium* taeniosis and cysticercosis are present in India, the disease is not widespread in India. The under-reporting of the disease in India is due to lack of attention to this neglected disease and lack of systematic population-based studies. There are wide variations in the frequency of cysticercosis in India which depends on geography, ethnicity, religion rituals, income, food habits, personal hygiene, level of education and standards of living, which are likely to influence the disease burden.

Only few cases have been reported from Kerala, where the literacy and standards of hygiene are high, and from Jammu and Kashmir, being a Muslim majority state consumption of pork is prohibited by religion. Also NCC was largely underreported due to lack of advanced diagnostic techniques like 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). Mahajan *et al.* (1982) [54, 57] reported the prevalence of taeniosis from 0.5-2% in hospitalized patients in northern India. With the advent of CT and MRI, the proportion of NCC in seizure disorders has dramatically increased. Sawhney *et al*. (1996) and Rajshekhar *et al*. (2006) [88] reported cerebral cysticercosis in 31% and 28.4% of patients respectively, in whom CT was done.

Cysticercosis is more prevalent in the northern States of Bihar, Uttar Pradesh and Punjab than rest of India. Prasad *et al*. (2007) [83] conducted a study based on 30 cluster sampling approach suggested by WHO, in the rural pig farming community of Mohanlalganj block, Lucknow district, Uttar Pradesh which revealed the prevalence of taeniosis of 18.6%; age above 15 years, history of passage of *Taenia* segment in stool, undercooked pork consumption and poor hand hygiene

were the factors associated with taeniosis. 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. Prasad *et al.* (2008a) [80] studied the risk factors for NCC clustering. Family history of epilepsy and lack of separate place for pig were identified as risk factors. 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) [80, 78]. 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) [98].

Khurana *et al.* (2006) [46, 47] conducted a comparative analysis for the prevalence of anti- cysticercus antibodies in urban, rural and slum population in and around union territory of Chandigarh. Anti-cysticercus antibodies were found in 17.3% cases with slum areas having highest prevalence of 24%; however only 8% of the sero-postive cases had previous history of seizure. Overall female showed the highest anti-cysticercus response of 20.4%. Parija *et al.* (2005) [72] reported Cysticercosis sero-prevalence of 6.5% among the healthy blood donors from Pondicherry was using both antigen and antibody detection methods. The treatment gap in rural India is above 90% (Prasad *et al.*, 2008b) [84] 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.

Kotokey *et al.* (2006) [48] studied 51 patients admitted Assam Medical College, Dibrugarh over a period of one year from April 2002 to March 2003 and the maximum incidence of neurocysticercosis was found in the age group between 21 and 30 years (43.41%). 100% of patients had clinical presentation of seizures. 21.56% patients (11) had ring enhancing lesions with central scolex. 78.44% (40) patients showed only ring enhancing lesions. ELISA test showed a sensitivity of 82.60% and specificity of 100%, while patients with CT scan features of neurocysticercosis had a sensitivity of 78.43% with ELISA.

Parija *et al.* (2009) [73, 95] determined the prevalence of cysticercosis among HIV patients residing in Puducherry and its neighboring districts of Tamil Nadu State, India. Out of 100 blood samples collected from HIV seropositive cases visiting JIPMER hospital, Puducherry, from June 2007 to May 2008, 2 HIV seropositive cases were found positive for anti-*T. solium* larval stage antibody by EITB and 4 were positive by ELISA. Only a single sample was positive by both EITB and ELISA. No serum sample was found positive for *T. solium* larval stage antigen by Co-A test. The overall seropositivity detected by all the methods was 5% in this study group.

Sahu *et al.* (2009) [95] evaluated ELISAs using metacestode somatic and ES antigens of *T. solium* for detection of anti-*T. solium* metacestode IgG antibodies in serum and cerebrospinal fluid (CSF) to observe a relation between live stage of the parasite and detection of antibodies in sera and CSF of NCC patients by ELISA using ES antigens. The sensitivity of the IgG ELISA using ES antigen is observed to be much higher in serum (88.2%) than in CSF (64.28%) although it is only marginally higher in serum (76.4%) than in CSF (75%) when somatic antigen is used in the ELISA. Whereas, the specificities of the ELISA using either somatic or ES antigen for detection of IgG antibodies in serum (97.97%; 96.96%) and CSF (96.42%; 97.61%).

In a community-based study conducted by Goel *et al.* 2011 [33] in the state of Uttarakhand, 141 cases of active epilepsy were detected giving a crude prevalence rate of 1% out of 14,086 individuals studied. On further examination of all the suspected cases of epilepsy using contrast computed tomography (CT) scan and electroencephalography (EEG), prevalence rate of epilepsy due to NCC was found to be 6.5/1000.

Sahu *et al.* (2015) [96] performed serum IgG ELISA on 40 clinically diagnosed ophthalmic cysticercosis (OCC) cases caused by *Taenia solium* larval infection in eye. The predominant site of infection was found to be extra ocular muscle where ocular motility disorder was the major clinical presentation. ELISA using larval somatic and excretory secretory (ES) antigens was positive in 32.5% and 45% cases respectively. Anti ES antibodies were detected more frequently in cases having extra ocular cysts compared to intraocular location.

Prudhivi *et al.* (2015) [85] studied the prevalence of NCC among patients attending a rural Hospital, Chinakakani, and South India. Out of 66 patients presented with manifestations of NCC, radiological evidence was found in 43 (65%) patients of which 27 (62.8%) showed single lesions and 16 (37.2%) showed multiple lesions. Out of 43 patients, majority of them were positive 40(92%) for CSF ELISA than Serum 28 (65.1%) ELISA while 19 (44.1%) were positive both for serum as well as CSF.

In a study carried out in Odisha, Sahu *et al.* (2015) [96] studied 64 patients presented with seizures in the age group of 5 to 50 years state using anti-Cysticercus IgG-ELISA. 18 of the total 64(28.12%) cases result were positive. Majority of the cases were being presented with a single space occupying lesion (n=41) whereas only 14 cases had >2 lesions based on CT scan. Normal CT was reported in 9 cases of which one case only appeared positive for anti-Cysticercus-IgG.

Swine cysticercosis in India

Cysticercosis is also highly prevalent among swine in India. Mahajan *et al.* (1982) [54, 57] found 8–10% of the pigs slaughtered in and around Chandigarh had cysticerci in their muscles and around 0.5% of the pigs reared in government farms were found to be infected. Ratnam *et al*., 1983 [90] observed 7% of the pigs in slaughtered in slaughter houses of Kolkata, West Bengal had cysticercosis. Prasad *et al.* (2002) reported 26% cysticercosis in swine from Mohanlalganj block, Lucknow district in the State of Uttar Pradesh with 40% of them having cysticerci in the brain.

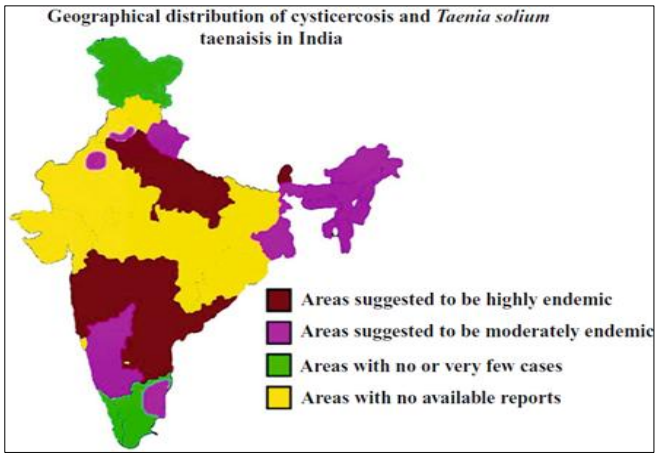

Fig 2: Adopted from Singh *et al.* (2012); Neurocysticercosis – Indian Scenario

Pathogenesis

Once eggs are ingested by humans, these hatch into oncospheres in the intestinal tract; oncospheres enter the bloodstream and are carried into the tissues of the host, particularly the brain. In brain most cysticerci lodge at the grey–white cortical junction. Cysticercus consists of two main parts, the vesicular wall and the scolex. Within the host, cysticerci generally live asymptomatically for prolonged periods because of various protective mechanisms of host tissues. Alvarez *et al.* (2008) [1] using murine models for cestode *Mesocestoides corti* suggested that role of certain glycoconjugates (GCs) released from parasite tegument rapidly when it penetrates into the CNS. Also partial loss of tegument and temporary reduction in the rate of tegument build up, causes less antigenic exposure during the early stages of parasite invasion. Carpio (2002) [7] observed Th2 response with increased production of Th2 cytokines in asymptomatic cases. Immunomodulation occurs through the production of alternately activated macrophages (AAMs). These AAMs promote the production of Th1 cytokines leading to activation of the alternative pathway which has also been suggested as an immuno protective mechanism of the parasite (Rodriguez-Sosa *et al*., 2002) [93]. Once the parsite dies, this balance ends and an adverse inflammatory reaction ensues with predominance of Th1 cytokines like TNF-α, IL-2 and IFN-γ. These cytokines through their effector mechanisms are responsible for severe neuropathology including the formation of granulomas (White *et al.*1997) [117]. The wall of blood vessels surrounding the parasites is invaded by inflammatory cells, leading to endarteritis with thickening of the adventitia, fibrosis of the media, and endothelial hyperplasia. The surrounding brain parenchyma also shows tissue changes, including brain oedema, gliosis, inflammatory infiltrates, and neuronal degeneration (Brutto and Sotelo, 1993)

Clinical spectrum

Clinical spectrum of the disease varies as per the localization of the cyst. Most common site reported in literature is brain parenchyma, followed by meninges, ventricles, eye and spinal cord. No sign or symptom is specific for NCC due to polymorphic manifestations. Commonest manifestation of human NCC is acute symptomatic seizures. Seizures are due to degenerating cysts or calcified granulomas and more rarely due to infarcts in patients with subarachnoid involvement (Del Brutto *et al.*, 1992) [17]. Other clinical conditions associated with NCC range from headache, hydrocephalus, chronic meningitis to focal neurological deficits, psychological disorders and dementia (Del Brutto, 1996; Carpio *et al.*, 1998; David and Mathai, 2000) [16, 12, 11]. In patients with extraparenchymal NCC hydrocephalus is the most common clinical symptom. Ocular and spinal cysts may also be characteristic if not diagnostic.

Besides, the clinical presentation also depends on the stages and number of cyst (Montano *et al*., 2005; Prasad *et al*., 2008a) [64, 80]. NCC might also influence the outcome of certain disorders due to its ability to modulate the host immunity like human cancers particularly glioma and haematological malignancies, and viral infections like Japanese encephalitis (JE) (Del Brutto *et al.*, 1997; Desai *et al.*, 1997; Herrera, 2000) [13, 19-20, 40]. Impaired cellular immunity in HIV infected individuals allows uncontrolled parasitic growth in multiple organs (Mauad *et al.*, 1997) [61]. HIV and NCC co-infection have been reported with unusual racemose/ giant cysticercal cysts (Garg and Kar, 2002; Delobel *et al.*, 2004) [32, 18]. Organ transplant recipients with NCC cases have also been reported (Gordillo-Paniagua *et al*., 1987; Bara Valencia *et al.*, 2002) [35].

Ophthalmic cysticercosis (intraocular) manifests symptoms like periocular swelling, proptosis, diplopia, restricted ocular motility, strabismus, decreased vision, lid edema, orbital cellulitis 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 pseudo hypertrophy. Subcutaneous cysticercosis is frequently asymptomatic but may manifest as palpable nodules.

Different stages of Neurocysticercosis

Neurocysticercosis (NCC) is a chronic disease with slow progression. Four stages of development and regression of the cysticercus in the CNS are recognized morphologically (Sharda *et al.*, 2002; Grag, 2002; Garcia *et al*., 2003) [105, 37].

1. Cystic or vesicular stage: It is viable parasite and is composed of well-defined, fluid-filled membrane, which contains scolex. Hence there is no host reaction.
2. Degenerating, colloid or granular stage: It corresponds to parasite death and associated inflammatory process. Parasite dies within 4-5 years in untreated cases, or earlier with treatment and the cyst fluid becomes turbid and appears eosinophilic. The components of the bladder and scolex are in different stages of degeneration and tissue around have multinuclear giant cells, foamy macrophages, and neutrophils. As the membrane becomes leaky oedema surrounds the cyst and necrosis occurs in the surrounding neural tissue in some cases.. This is the most symptomatic stage.
3. Granular nodular stage: In this stage fibrosis develops with time, progressively occupy the entire lesion. Oedema decreases as the cyst retracts further. This stage can be macroscopically recognized as a nodule of smaller size than the bladder in the nodular stage.
4. Nodular calcified stage: The fibrous nodule thus formed undergoes mineralization and subsequently calcification. Thus end-stage quiescent calcified cyst remnant is formed.

Diagnosis of Neurocysticercosis (NCC)

The diagnosis of NCC is difficult due to its variable clinical presentations. Probable diagnosis can be based on clinical and epidemiological criteria (Del Brutto, 2001; Garcia *et al.*, 2005). Definitive diagnosis is by direct demonstration of the parasite in tissues or radiological demonstration of scolex in cystic lesions using neuroimaging modalities. In India, NCC needs to be differentially diagnosed from certain conditions like presence of fungal and tubercular granulomas which present large number of single small enhancing CT lesions (SSCTL) (Garg 2002; Garg and Kar, 2002) [32].

Serological techniques

Many serological techniques have been used for diagnosis and epidemiological studies of cysticercosis. As with most of the tests that use unfractionated antigens, these are associated with low sensitivity and specificity (Ramos-Kuri *et al.*, 1992). Mahajan and colleagues were first to establish serological techniques, complement fixation test (CFT) and indirect haemagglutination test (IHA) for the diagnosis of cysticercosis (Mahajan *et al.*, 1974; 1975; 1982). These workers found that the metacestodal antigens were more sensitive than the antigens from the adult worms. Also IHA test was found to be more sensitive and specific than the CFT.

Malla *et al*. (1992, 2005) [58, 59] compared the efficacy of ELISA and IHA for the diagnosis of NCC and found that the IHA technique was more specific for the detection of antibodies in cerebrospinal fluid (CSF) samples while cross reactions were observed with ELISA. Parija and Reddy (2006) [71] used co-agglutination (Co-A) test for diagnosis of NCC in Puduchery, South India and found it to be moderately sensitive and specific.

Elisa

Although Serum based ELISA is not considered as diagnostic test for NCC, however it is very much in use due to ease of the procedures involved. Three antigenic fractions from cysticerci have been 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% (Flisser *et al.,* 1975) [26]. Later, Ito *et al.* (1998) [41] had shown that the cyst fluid gave less back ground reactivity. Prabhakaran *et al.* (2004) [77] recently reported sensitivity 80% and specificity 94% for solitary cysticercus granuloma (SCG) by using ELISA employing the lentin-lectin affinity purified cyst fluid antigen.

Enzyme electro immune transfer blot

The use of enzyme electro immune transfer blot (EITB), commonly known as Western blot (WB), was first published in 1986 for NCC (Gottstein *et al.,* 1986) [35]. 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) [111]. Later the sensitivity was found to be related to the number of cysticerci in the brain: 98% sensitivity for cases with three or more cysticerci, while only 65% sensitivity in patients with one or two parasites (Wilson *et al*., 1991; Plancarte *et al.,* 1994, 1999) [119, 99, 74]. CSF samples give better results with EITB assay than serum. This test is commercially available currently and is also used as a criterion for diagnosis of NCC (Del Brutto *et al.,* 2001).

Lymphocyte transformation test

Using the principle of lymphocyte transformation test (LTT), a new diagnostic method has been established recently (Prasad *et al.,* 2008c) [81]. The test has shown a very good promise for the diagnosis of NCC with high sensitivity (93.7%) and specificity (96.2%). Even in case of single cyst infection the sensitivity of the test was 87.5%, which is much higher compared to EITB or ELISA. In its present form, the procedure can be performed at reference laboratory only owing to use of radioactive thymidine (3H-TdR) to measure the cell proliferation; however, there is potential for the test to be modified to non-radioactive technique like bromodeoxyuridine-ELISA LTT that can be used in general laboratories.

Neuroimaging techniques

The advent of neuroimaging techniques such as CT and MRI has greatly improved the accuracy in the diagnosis of NCC (Sharda *et al.,* 2002; Garcia *et al.,* 2003) [105, 30]. The accuracy of diagnosis depends on the type of cysticercus, developmental stage and involution, and location and number of cysts. Imaging findings in all four stages described earlier reflect underlying changes in the disease process and host response. 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 neuroimaging tool for the diagnosis of degenerating and innocuous (viable) cysticerci, while CT is the best for calcified lesions (Garcia *et al.* 2003) [30]. The added advantage of MRI over CT scan is its ability to differentiate the stages of the parasite, which CT is not able to do. In addition, MRI with gradient echo sequence phase imaging has been reported to be 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) [38]. Although MRI allows better detection of the active parasites but some calcified parasites may be missed, especially in absence of gradient echo sequence.

DNA-based methods

PCR based methods have been developed for detection of species-specific parasite DNA (Lightowlers *et al.* 2016) [52]. PCR-based methods have major advantage of being highly sensitive and specific and applicable even to stool samples (copro PCR), as well as the high throughput as compared to microscopy. When used in combination with microscopy, copro PCR further improves sensitivity (Yamasaki *et al.,* 2004) [121].

A multiplex PCR developed using amplification of cytochrome c oxidase subunit I (cox1), provides for species-specific diagnosis by yielding evident differential products unique for *Taenia saginata* and *Taenia asiatica* and for American/African and Asian genotypes of *Taenia solium* with molecular sizes of 827, 269, 720, and 984 bp, respectively and has been tried in a study at the community level (Yamasaki *et al.* 2004) [121]. Praet *et al*. (2013) [79] have developed a real-time multiplex PCR by using ITS 1 of the ribosomal RNA, while Mayta *et al.* (2008) [62] have developed a nested PCR approach utilizing the Tso31 gene. Although nested PCR approach has increased sensitivity when tested on stool samples and has an advantage over other PCR-based detection methods but it is not used as mass detection tool due to technical complexity and expensiveness. Difficulty in parasite DNA extraction and the presence of enzyme inhibitors in stool are other serious drawbacks (Nunes *et al.* 2006) [68]. In order to overcome these limitations, Nkouawa *et al.* (2010) [67] developed a loop-mediated isothermal amplification (LAMP) test targeting cathepsin L-like cysteine peptidase (clp) and cox1 genes. LAMP assay has advantage of low equipment requirement and the ability to differentiate between *Taenia* species (Nkouawa *et al.* 2012) [66]. The method has been applied to a field survey to amplify DNA extracted from proglottids technique (Nkouawa *et al.* 2012) [66]. The specificity of the test needs to be validated further.

Treatment of Neurocysticercosis

Albendazole and praziquantel are the two main cysticidal drugs used for the treatment of NCC and have been found to be highly effective to destroy the cerebral parenchymal cystic lesions. Albendazole has been reported to have better efficacy than praziquantel. Besides, Albendazole is less expensive, safer and penetrates better into the subarachnoid space. Also, the bioavailability of albendazole is increased by co-administration of steroids (Jung *et al*. 1990) [43] and is not affected by phenytoin or carbamezepine, but in case of praziquantel bioavailability is decreased by co-administration

of steroids (Vazquez *et al.* 1987) [112], as well as by phenytoin and carbamezepine (Bittencourt *et al.* 1992) [5], which are often used as first-line anticonvulsants in children with seizures due to NCC. Albendazole is reported to be more effective in subarachnoidal, ventricular and spinal cysticercosis, and frequently obviates the need for surgery.

Usefulness and safety of anticysticercal treatment has been debatable (Singh and Sander, 2004) [106, 107]. Opponents argue that effectiveness of anticysticercal therapy is possibly a reflection of natural course of the disease and even if left untreated, cysticercal lesions either disappear spontaneously or are calcified (Mitchell and Crawford, 1997; Kramer *et al.*, 1989) [63, 45]. Anticysticercal therapy may also aggravate cerebral oedema, produce vasculitis and stroke, which may even lead to death. To minimize these complications, corticosteroids are administered concomitantly, especially in case of massive parasitic load. Anticysticercal treatment is avoided in patients with cysticercotic encephalitis (Del Brutto and Sotelo, 1988; Carpio *et al.*, 1998) [12, 8]. There is strong consensus that there is no role for antiparasitic drugs in patients with only calcified lesions (Riley *et al.*, 2003) [92]. Antiparasitic therapy is strongly recommended by most experts in patients with multiple subarachnoid cysticerci or giant cysticerci.

Role of surgery

Surgical intervention is required in some cases particularly in intraventricular and subarachnoid NCC. A ventriculoperitoneal shunt is needed for hydrocephalous along with simultaneous use of steroids and albendazole and recurrent courses of steroids reduce the risk of frequent obstructions and shunt revisions. Endoscopic removal of cysts being the least invasive is the procedure of choice (Goel *et al*. 2008; Suri *et al*. 2008) [34, 110]. Excision of giant cysts that fail to respond to medical therapy may be required.

Prevention and control

Cysticercosis has been categorised as a potentially eradicable disease. The main focus of control in developed countries has been the eradication of swine cysticercosis through advanced animal husbandry practices and meat inspection procedures. The approach has been successfully implemented in the United States and Western Europe (Ferreira *et al.* 1997) [23]. A small number of carriers of tapeworm infection with tapeworm may infect vast numbers of healthy human beings. Thus tapeworm carriers are potential target for the control of cysticercosis/taeniosis. In the developing world, emphasis has been laid on control of the parasite through health education and mass administration of anthelminthics in endemic areas to remove tapeworm carriers (Plancarte *et al.* 1999; Garcia *et al.* 2003; Lightowlers, 2003) [74, 30, 51]. Education on proper community-based sanitation, building and usage of latrines that are inaccessible to pigs, proper disposal of human night soil and education on community-friendly pig rearing (restraining pigs, vaccination programs) are indispensable as free access of pigs to human faeces plays a crucial role in the maintenance of the life cycle of *T. solium* cysticerci. Furthermore, improved meat inspection procedures as well as controlled slaughter and educating farmers about identification of infected pork may be helpful. Personal hygienic measures has to be advocated as it can prevent human cysticercosis acquired through the faecal-oral route after contact with a tapeworm carrier, contaminated water or food (Winkler *et al.*, 2009) [120]. Cysts die if meat is stored at 4°C for more than 1 month, or -20°C for 1–3 days (Sotelo *et al.* 1986) [109]. Irradiation using doses between 20 and 60 krad of gamma-radiation has been found render carcasses infested with cysticercosis fit for human consumption (Verster *et al.*, 1976) [114].

Vaccination

Although there are many reports of the success of a few proteins in vaccination of porcine cysticercosis, no effective vaccine has been developed till date against the *T. solium*. Several factors like the complex immunology of the parasite, occult nature of this infection and the minimal morbidity associated with this infection, make taeniosis a poor candidate for vaccine development. Thus at present vaccination against taeniosis does not, therefore, appear to be immunologically or logistically feasible. Vaccinating pigs in endemic region may be good strategy to prevent porcine cysticercosis and to improve animal health, meat yield and to break the parasite life cycle, preventing taeniosis and consequently preventing human cysticercosis.

In laboratory and field studies, varieties of antigens have been tested and have demonstrated effective partial protection (Lightowlers, 2003) [51]. In New Zealand Rickard *et al.* (1995) [91] have developed a commercially viable vaccine using recombinant antigen from *Taenia ovis* oncosphere-stage. As the immune response to *T. solium* is similar to *T. ovis*, it should also be possible to develop an effective vaccine to prevent both human and swine cysticercosis (Mitchell and Crawford, 1997) [63]. Two different oncosphere antigens, designated TSOL18 and TSOL45 were evaluated by Lightowlers (2004), each of which induced complete or near complete protection against experimental challenge infection in four separate vaccine trials in pigs. The vaccine containing TSOL18/TSOL45 thus has the potential to make a substantial contribution to the control and, potentially, the eradication of human neurocysticercosis.

Conclusions

Cysticercosis is a serious public-health problem especially in resource poor and developing countries including India. It is considered as a “biological marker” of social and economic development. Due to lack of systematic population-based studies in most parts of the country; it is difficult to estimate the disease burden in India. However, few recent studies especially after advent of better diagnostics like 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%. As cysticercosis is a largely considered preventable and eradicable disease, appropriate corrective measures like health education to susceptible people, better medical facilities, mass awareness and treatment of *T. solium* carriers, and proper meat inspection and proper treatment of measly pork may help to reduce the disease burden considerably in the endemic areas.

Future challenges and solutions

CDC Working Group on Parasitic Diseases has identified NCC as a potentially preventable and eradicable disease. Hence emphasis should be more on personalized therapy rather than that based on generalizations. To know about the exact burden of disease in community, more systematic studies need to be undertaken. Community-based programs are needed to study the control in transmission and propagation of the parasite by use of existing conventional drugs, especially in endemic regions of the world. Search and development of new drugs and alternate medicines for therapy

have ample scope and should be encouraged. No vaccines have been developed and no new drugs are currently under trial. Some proteins in the vaccination of porcine cysticercosis as reported by some research groups have given encouraging results, but this needs further rigorous studies and investigations. There is need for establishment of research, new approaches, novel tools and promoting the concept of "one health" through the development of integrated control programme for NCC.

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