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Review Article

Neurocysticercosis: A disease of neglect

Abhishek Mewara, Kapil Goyal, Rakesh Sehgal

Department of Medical Parasitology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

KEY WORDS

Neglected tropical disease, neurocysticercosis, *Taenia solium*

ABSTRACT

Neurocysticercosis (NCC) is a neglected tropical disease caused by larval forms of the parasite *Taenia solium* lodging in central nervous system (CNS). There is a huge morbidity and debilitation due to CNS manifestations of NCC in developing and underdeveloped regions of the globe, mainly Asian, African and Latin American countries. It is the cause of epilepsy in about 1% of the population of endemic countries and is the underlying etiology in about 15-50% persons with epilepsy, depending upon the geographical region. There is no perfect diagnostic method and the diagnosis relies on a combination of clinical, radio-imaging, immunologic and epidemiologic data. Treatment includes anti-parasitic treatment by cysticidal drugs and management of associated symptoms and complications. The disease is eradicable and control depends on an integrated and coordinated involvement of international bodies like the World Health Organization along with scientific institutions and political and administrative strata of the endemic countries to provide the essential tools such as adequate sanitation, live-stock management, health education and improved socio-economic conditions.

INTRODUCTION

Cysticercosis, caused by metacestodes of *Taenia solium*, a two-host zoonotic cestode of the order cyclophyllidea, is a disease of antiquity. The ancient vedic texts describe infestations of head and eyes by parasites and Greek physicians Hippocrates and Theophratus were aware of human infection with a tape worm.[1,2] The name "cysticercosis" was given by Laennec derived from the Greek word "Kystic" meaning bladder and "Kercos" signifying tail. In 1809, Rudolphi gave the second name of "cellulose" due to its great affinity for connective tissue and in 1853, Beneden was the first to suspect its relationship to *Taenia* worm.[2] Humans acquire cysticercosis through feco-oral contamination with *T. solium* eggs from tapeworm carriers.[3] Though, cysticerci (larval cysts) can develop in any organ in the body, cystercerci in the brain or spinal cord, neurocysticercosis (NCC) is the most serious form of infection.

Cysticercosis is of much economic and public health importance causing morbidity and mortality in many developing countries of Asia, Africa and Latin America.[4] Until recently, NCC and echinococcosis were referred to as "neglected" diseases, but are now recognized by the World Health Organization (WHO) as "major neglected diseases".[5,6] It is one of the most common parasitic diseases of the central nervous system (CNS) and is considered a "biological marker" of the social and economic development of a community. In many endemic communities, NCC is the cause of epilepsy in about 1% of the population.[5] It the past few decades, it has gained even more importance as it has spread to areas previously unknown to be endemic like the United States of America (USA) and Australia. This epidemiological diversity can be attributed to intensification of animal

Address for correspondence
Dr. Rakesh Sehgal,
Department of Medical Parasitology, Postgraduate Institute of Medical Education and Research, Chandigarh - 160 012, India.
E-mail: sehgalpgi@gmail.com

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products, increase in world meat and live animal trade, large scale intra-and inter-country migration of agricultural and other workers such as domestic employers and international tourism.[7,8]

EPIDEMIOLOGY

The disease is world-wide in distribution, though major endemic regions are the world's poorer countries where families raise free-roaming pigs that are able to ingest human feces.[5,9] These regions include Latin America, most parts of Asia (including China and the Indian subcontinent), Eastern Europe and most of Africa. The world-wide prevalence of NCC still remains to be known, though, initiatives are underway to determine the burden in endemic countries as well as in developed nations like USA.[9,10-12] The data on the burden of NCC associated with epilepsy is relatively well-documented, hence is used to provide estimates of prevalence and incidence of NCC in endemic regions.[9,10] The estimated numbers of people suffering from epilepsy due to NCC are as high as 0.31-4.6 million in sub-Saharan Africa, 0.45-1.35 million in Latin America, 1 million in India and 0.3-0.7 million in China.[5] In a community-wide screening survey from rural Peru, the seroprevalence was 24% and was associated with seizures with an odd's ratio of 2.1,[13] with an additional 13% of those with negative serology demonstrating calcifications typical of NCC in computed tomography (CT) scans, thereby giving an overall estimate of 37% prevalence of cysticercosis.[5,13] Estimates of prevalence from other Latin American countries range from 15% to 38%.[5] In a systematic review conducted to estimate the frequency of NCC world-wide, the proportion of NCC among persons with epilepsy was consistently found to be about 29% (95% CI: 23.5-36.1%) from Latin America, sub-Saharan Africa and Southeast Asia.[10] The average incidence of *T. solium* infection in China has been estimated to be 0.11%, with 1.26 million suffering from teniasis and 3-6 million from cysticercosis.[6]

In the Indian subcontinent, the disease is documented to be endemic in India, Bhutan, parts of Indonesia (Bali and Papua), Nepal and Timor-Leste. In India, it is prevalent in all states, with WHO estimating NCC to be the cause of epilepsy in up to 50% of Indian patients who present with partial seizures; ocular cysticercosis also being common.[6] In a community survey in Vellore in southern India, among those suffering from active epilepsy, NCC was found in 28% by CT scan and 13% by the enzyme-linked immunoelectrotransfer blot (EITB). Overall, 34% of patients were diagnosed with NCC. Moreover, there was no significant difference in prevalence of NCC in urban and rural areas.[14] In Puducherry in south India, seroprevalence was observed to be 16% in patients with epileptic seizures[15] and 6% in blood donors when tested for both antibodies and antigens.[16] In Chandigarh in northern India, overall seroprevalence in the general population was found to be 17%, with 24% in slum areas, 20% in rural and 8% in organized urban sectors, with only 8% of the seropositive individuals having history suggestive of NCC.[17] Another study carried out in a rural pig farming community across 30 villages in north India showed a very high prevalence with 48% of those suffering from active epilepsy fulfilling the definitive or probable diagnostic criteria for NCC; epilepsy in the family and no separate place to keep pigs being the major risk factors.[18]

DISEASE

Human beings acquire cysticercosis through feco-oral contamination with *T. solium* eggs from tapeworm carriers.[3] Thus, vegetarians and other people who do not eat pork can acquire cysticercosis; exogenous autoinfection due to ano-oral contamination and endogenous autoinfection due to reverse peristalsis can also give rise to cysticercosis. After ingestion of eggs, the oncospheres are liberated in the duodenum, can penetrate the intestinal mucosa and enter the local lymphatics and mesenteric vessels and may migrate to locate anywhere in the body as larval cysts.[19] Within 2-3 months, the oncospheres lose the hooks and develop into fluid filled bladder worms or cysticerci. The most frequent site of cysticerci is subcutaneous and intramuscular tissues, followed by the brain and eye. These can also occur in heart, liver, lung, abdominal cavity and rarely spinal cord. Symptomatic disease results almost exclusively from invasion of the nervous system, i.e., NCC and the eye; there are case reports, though, of extraneural forms presenting as cystic masses involving skeletal muscles, subcutaneous tissues, buccal mucosa, tongue and lips[20,21] and rare cases of disseminated cysticercosis.[22]

NCC is polymorphic in clinical presentation and ranges from asymptomatic individuals to cases with severe neurological problems. The infected persons grossly vary in terms of the number of active episodes and recurrences, incidence of serious complications, as well as incidence of co-infections with Japanese Encephalitis and HIV.[23] Carabin *et al.* systematically reviewed estimates of frequencies of different manifestations, complications and disabilities associated with NCC and documented about 79% having seizures/epilepsy, 38% severe headaches, 16% focal deficits and 12% signs of increased intracranial pressure; all other manifestations such as cranial nerve palsy, gait abnormality/ataxia, focal deficits, visual changes, altered mental state/psychiatric symptoms and pyramidal signs occurring in lesser than 10% of symptomatic NCC patients.[24] The clinical presentation is clearly different in parenchymal

and extraparenchymal NCC. The most common presentation of parenchymal NCC is with seizures, while extraparenchymal NCC may cause hydrocephalus by mechanical obstruction of the ventricles or the basal cisterns.[19,25,26]

NCC is common in adults as well as in children. Although it usually manifests after 5 years of age, symptomatic NCC is seen even in infants and preschool children. The prevalence of epilepsy in Mexico was seen to increase with age.[27] There are also age-related differences in the manifestation of NCC. Most of the cases of childhood NCC present with mild to moderate symptoms and single lesions and extraparenchymal NCC seen in adults are rarely seen in children.[28] There is also clinical heterogeneity across countries; most cases from the Indian subcontinent present with single degenerating lesions, whereas those from Latin America and China present with few viable lesions.[29] Extraparenchymal NCC is frequently seen in Latin American countries, whereas it is uncommon in the Indian subcontinent. These variations are perhaps due to complex interactions between the host, parasite and environmental factors.[30] Genetic differences in *T. solium* cysticerci have been reported from different countries and may contribute towards the clinical variations across countries.[31] A significantly increased frequency of HLA-A28 (39% vs. 15%) and decreased frequency of HLA-DQW2 (4% vs. 31%) has been reported from a Mexican cohort with parenchymal NCC when compared to healthy controls, with a relative risk of 3.5 for developing the disease in HLA-A28 positive individuals.[32] From India, in patients with single, small, contrast enhancing CT lesions, a positive association of HLA-DRB1* 13, HLA-B63 and HLA-B58 and a decrease in persons with HLA-A11 has been shown.[33,34] The environmental factors determining solitary cysts are young age and a patient being from the Indian subcontinent or travelers from non-endemic countries. Such patients are usually young teenagers or young adults (majority under 20 years of age) presenting with newly developed seizures.[35,36] Though not clearly known, the factors responsible could be that in India only a few individuals raise pigs and a vast subgroup is vegetarian or not eating pork.[35] The cooking habits in India where heating the food to high temperatures is commonly practiced, in contrast to South American countries and China where undercooked food is commonly used in recipes, may also be aiding milder egg challenges and thus low parasite loads and milder infections.

DIAGNOSIS

The lack of specificity of the neurological symptoms makes it impossible to diagnose the disease on clinical grounds alone. Thus clinical presumptive diagnosis is usually substantiated with radio-imaging techniques and serodiagnosis. An ideal test for diagnosis of NCC should be a non-expensive, simple-to-perform, point-of-care method with good sensitivity and specificity not only for multiple lesions but also for solitary cyst lesions. Such method is not yet available; hence the diagnosis depends on objective clinical, radio-imaging, immunologic and epidemiologic data, the only absolute diagnostic criteria being histologic demonstration of the parasite from biopsy of the brain or spinal cord, cystic lesions showing scolex on CT or magnetic resonance imaging (MRI), or direct visualization of subretinal parasites by funduscopy [Table 1].[19]

Neuroimaging

In most cases, NCC diagnosis is based on neuroimaging studies (CT and MRI). CT and MRI also provide

Table 1: Diagnostic criteria for NCC*

Absolute criteria
- Histologic demonstration of the parasite (scolex with its suckers and hooks, or the presence of parasitic membranes) from biopsy of a brain or spinal cord lesion
- Cystic lesions showing the scolex (bright nodule within the cyst) on CT or MRI
- Direct visualization of subretinal parasites (usually located over the macula, yellowish in color with a central dark spot) by fundoscopic examination

Major criteria
- Lesions highly suggestive of NCC (cystic lesions without a scolex, single or multiple ring or nodular enhancing lesions, and parenchymal round calcifications) on neuroimaging studies
- Positive serum EITB for detection of antibodies to glycoprotein antigens
- Resolution of intracranial lesions (disappearance or calcification) after therapy (albendazole or praziquantel)
- Spontaneous resolution of small (<20 mm) single enhancing lesions

Minor criteria
- Lesions compatible with NCC on neuroimaging studies (hydrocephalus or abnormal enhancement of the leptomeninges, multiple filling defects in the column of contrast medium in myelogram)
- Clinical manifestations (seizures/epilepsy, focal deficits, increased intracranial pressure, and intellectual deterioration) suggestive of NCC
- Positive CSF ELISA for detection of anticysticercal antibodies or cysticercal (excretory-secretory) antigens
- Cysticercosis outside CNS (a. Histologic demonstration from biopsy of a subcutaneous nodule. b. X-ray showing multiple "cigar-shaped" calcifications in thigh and calf muscles. c. Direct visualization of a cysticercus in anterior chamber of the eye)

Epidemiologic criteria
- Evidence of a household contact
- Individuals coming from or living in an area where cysticercosis is endemic (sub-Saharan Africa, Latin America, most parts of Asia including China and the Indian subcontinent)
- History of frequent travel to disease-endemic areas

*Adapted from reference 19. NCC: Neurocysticercosis, CT: Computerized tomography, MRI: Magnetic resonance imaging, CNS: Central nervous system, CSF: Cerebrospinal fluid, EITB: Enzyme-linked immunoelectrotransfer blot, ELISA: Enzyme-linked immunosorbent assay

information about the parasite stage and location.[37,38] Three main stages have been described: Vesicular (viable), colloidal (degenerative) and calcified (inactive).[39] CT is the best radiological method for detection of intraparenchymal calcification, while MRI is more sensitive for the identification of cysts in the ventricles.[7] Radioimaging methods may serve the useful purpose, but due to the unavailability of the facilities at many cities and high cost, its use is limited in the developing countries. Moreover, imaging findings may mimic with other types of neurological diseases, thus posing problems in the diagnosis.[40,41] In some cases, particularly when parasites are located in the subarachnoid basal cisterns, neither CT nor MRI can detect the parasite. In these cases, NCC diagnosis is supported by clinical, epidemiological and serological data as well as by the response to cysticidal treatment.[42]

Immunodiagnosis

Immunodiagnosis of NCC by detecting an antigen and/or antibodies is an accessible, low-cost diagnostic tool in areas of endemicity.

Antibody detection

A variety of immunodiagnostic techniques and antigens (total metacestode soluble antigens, metacestode membrane or scolex soluble extracts, semi-purified proteins) have been assessed for the diagnosis of NCC with variable sensitivity and specificity.[43-48] It has been observed that immunodiagnostic tests based on crude antigen preparations have, at best, moderate sensitivity and specificity.[49] Using semi-purified/purified antigens could constitute a better alternative, but purification procedures are often complex and require considerable technical expertise.

Currently, the most reliable immunological test is an EITB assay with serum samples using lentil lectin glycoprotein antigens of *T. solium* cysts and is reported to have a 100% specificity for detection of antibodies in serum and cerebrospinal fluid (CSF).[7,50] Although, 90% sensitivity has been reported in patients with more than two lesions, it declines to 50-62% with a single lesion and for calcified lesions.[51] It is also estimated that most cured patients remain seropositive when followed-up for 1 year after anti-parasitic therapy, mainly due to persistence of antibodies after resolution of active infection.[52] Extraneural cysticercosis and cross-reactions with other cestodes and helminths can also contribute to false-positive results obtained by using serum antibodies.[52,53] Atluri *et al.* have shown a high sensitivity (100%) in all the thirteen NCC seropositive children (11 had solitary NCC lesion and 2 had multiple NCC lesions) and 60% sensitivity among suspected cases of NCC children who were seronegative for NCC (36% had solitary NCC lesion and 24% had multiple NCC lesions), with specificity of 92% by two-dimensional polyacrylamide gel electrophoresis EITB.[54] This could be a useful diagnostic modality in endemic countries for the serodiagnosis of NCC, however it requires expertise and facilities. EITB has been extensively used for diagnosis of human and porcine cysticercosis and is commercially available.[55] The drawback, however, is that it depends on infected pigs for supplying the source material. Preparation of the antigen and performance of western blot require considerable technical expertise. Furthermore, batch differences can exist between different antigen preparations and the antigen mixture is not suitable for use in an enzyme-linked immunosorbent assay (ELISA) format due to the presence of non-specific fractions. Further, a western blot assay is not suitable for field studies, nor is it a suitable or affordable assay for diagnosis in countries where cysticercosis is endemic.[56]

The development of numerous serodiagnostic tests using different parasitic antigens is indicative of the fact that none of them is 100% sensitive and specific, particularly in single-lesion parenchymal NCC. Michelet *et al*. compared the diagnostic efficacy of EITB and HP10 antigen detection by ELISA and found the sensitivities of antibody detection by both tests not to be significantly different, with ELISA identifying HP10 even when vesicular cysticerci were located in the subarachnoideal basal cisterns.[57] Other tests like dot-blots have also been used for the serodiagnosis of several parasitic infections and can give sensitivities as high as those observed with ELISA, at the same time being rapid, easy to carry out and read. Mandal *et al.* have shown that ELISA and dot-blot assays developed "in-house" can give good sensitivity in the detection of anti-cysticercal IgG, especially among the pediatric cases of NCC who have multiple brain lesions (100%) when compared to those with single-lesion (87%).[58]

Antigen detection

Antigen detection assays have also been described. The detection of secreted cysticercal Ag by ELISA is highly sensitive and specific for the diagnosis of living cysticerci (vesicular) localized in the subarachnoideal space at the base of the skull.[59,60] Antigen detection assays also permit monitoring and follow-up of anti-parasitic treatment.[39] Though the antigen detection reflects the presence of viable parasites, but a positive antigen detection test is no definitive indication of active NCC, because cysts can be located outside the CNS. Fleury *et al.* have shown the detection of secreted cysticercal antigen in CSF a useful tool for the diagnosis of inflammatory NCC.[60] Sensitivity was shown to be higher in cases with inflammation compared to non-inflammatory disease (94% vs. 33%) and in cases of multiple- compared with single-cyst cysticercosis (85% vs. 33%). Thus, antigen positivity is a

strong indicator of active, inflammatory, multiple-cyst NCC.[60] Garcia *et al.* evaluated the utility of circulating parasite antigen in sera of patients with hydrocephalous secondary to NCC.[61] The assay gave positive results in 48% of patients with hydrocephalus, but was consistently negative in patients with calcifications. A study from Peruvian individuals demonstrated the sensitivity of 86% for detection of antigen in CSF by ELISA.[62] Negative results were restricted to patients with only a single live cyst or only enhancing lesions. Thus, though the sensitivity was high in multiple cystic lesions, but it had poor diagnostic value in patients having single cyst.

Most of the immunodiagnostic tests need elaborate standardization and cannot be performed with ease at rural areas and underdeveloped regions where the actual burden of disease is present. This creates a necessity of exploration of simpler tests with/without use of non-invasive samples, which can be utilized for point-of-care service. Such tests have not, though, seen the light of the day to be truly useful for patient care in large scale settings. Simple and rapid latex-based agglutination test for detection of *T. solium* metacestode antigen in the CSF and serum has been evaluated for diagnosis of NCC exhibiting sensitivity and specificity of 64% and 85% and 52% and 96% in CSF and serum samples, respectively.[63] Non-invasive samples such as urine and saliva have also been evaluated for antigen detection. Parija *et al.* reported a sensitivity of 62% and specificity of 91% for detection of cysticercus antigen in urine specimens using a polyclonal antibody-based ELISA assay.[64] Castillo *et al.* reported 92% sensitivity of urine antigen detection for viable parasites, which decreased to 62% in single cyst patients.[65]

Molecular techniques

More recently, methods based on detection of cysticercal deoxyribonucleic acid (DNA) have been increasingly explored. Nucleic acid amplification techniques may provide an answer to the challenge of diagnosis of NCC by virtue of their high sensitivity and specificity, ability to detect parasite load and faster turn-around-time. Both conventional and real-time polymerase chain reaction (PCR) assays have been developed for diagnosis of NCC in CSF samples. In a study, using highly repetitive elements of the parasite as probes, as little as 10 fg of *T. solium* DNA has been detected by PCR in CSF of 96% patients.[66] A semi-nested PCR based on HDP2 able to detect 0.174 fg of *T. solium* DNA has been reported.[28,67] PCR based on pTsol9 amplification detected 90-100% of NCC cases depending on stage and location of the parasite, exhibiting 95% sensitivity and variable specificity (80% or 100%) depending on the controls used.[57] A real-time TaqMan based PCR has been developed targeting pTsol9 gene yielding a sensitivity of 92% and specificity of 100% in CSF samples from patients with definitive NCC.[68] There is a lack of literature regarding the usefulness of molecular diagnosis of NCC in patients with single lesions, in serum samples and whether parasite DNA load in CSF can be used for follow-up of NCC patients. Solitary NCC lesions are often missed by serological methods and laboratory confirmation of such cases is a major challenge. Thus detection of parasite DNA by PCR can aid in diagnosing cases, which are missed by available radiological or immunological tests.

Treatment

The treatment of NCC is controversial and despite several advances, the various therapies remain either suboptimal or based on empiric observations and subsequent refinements through clinical trials.[69] The treatment depends on anatomic location, stage of evolution, number of cysts, degree of inflammation, severity of disease and life-threatening complications which require emergency treatment. Both praziquantel and albendazole are proven cysticidal agents, though their effectiveness is variable and a single course of anti-parasitic therapy may not eliminate all cysts. A meta-analysis assessing the effect of cysticidal drugs on neuroimaging and clinical outcomes of patients with NCC concluded that with therapy there is better resolution of colloidal and vesicular cysticerci, with lower recurrence of seizures in patients with colloidal cysticerci and a reduction in the rate of generalized seizures in patients with vesicular cysticerci.[70] More randomized controlled studies are required in future studies to evaluate and identify more efficacious and safe anthelmintic agents, better combinations of agents and better regimens. Surgery plays a role in the treatment of complicated disease, in removal of easily approachable symptomatic cysts through neuroendoscopy, removal of large approachable cysts that are likely to lead to long-term exposure to immunosuppressives or anthelmintics by open surgery, or shunt placement for hydrocephalus.[69]

Prevention

NCC is a preventable and eradicable disease. The transmission of parasite is related to social, cultural and economic factors such as poverty, inadequate sanitation and close association of humans with pigs with access of pigs to areas used for defecation. Hence the control measures, which are certain to be effective are health education, improved socio-economic conditions and life-style changes, mass treatment of carriers, restricted sale of measly pork and full cooking of pork.[23] Another important measure to break the host-parasite transmission cycle is the development of vaccines targeting cysticercosis in pigs which are safe, effective, inexpensive and administrable in edible form. Flisser *et al.* have evaluated recombinant oncosphere antigens TSOL18 and TSOL45-1A to induce 100% protection in three independent vaccine trials in pigs in Mexico and

Cameroon.[71] Gauci *et al*. evaluated the recombinant antigens TSOL16, TSOL45-1A and TSOL45-1B and found TSOL16 to be capable of inducing high levels of immunity in pigs against a challenge infection.[72] Further studies are thus required for production of effective vaccines, which would aid in control and eradication of NCC.

CONCLUSION

NCC is an important cause of morbidity and mortality in humans. Being a disease of poor socio-economic strata, the approach toward control of this disease is multi-sectorial; the control requiring not just delivery of practical instruments of diagnosis, treatment and prevention by science, but also commitment at administrative and political level, which is required to improve basic health care infrastructure of endemic nations. A simple measure such as provision of adequate sanitary latrines to prevent indiscriminate defecation can effectively prevent millions of cases of epilepsy. Despite being the most common cause of adult-acquired epilepsy world-wide, the morbidity due to NCC is underappreciated and research is underfunded and hence the study of NCC lags behind most other major infectious diseases.[73] A balanced commitment of resources to develop more effective approaches that could lead to better treatment and control of the disease may be the key to improve the quality-of-life of millions of people.

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