

Neurocysticercosis: A Health Burden in Nepal

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Abstract

Neurocysticercosis is caused by the zoonotic parasite *Taenia solium*. In patients burdened by this disease epileptic seizures are common. The disability associated with this disease has been a health burden in general and particularly in Nepal. The clinical manifestations of neurocysticercosis include seizures, headache, cognitive dysfunction and focal neurological deficits. Computerized tomography scanning and magnetic resonance imaging techniques are most commonly used investigative tools for the diagnosis of NCC. Radio-imaging techniques combined with serological techniques such as enzyme-linked immune sorbent assay and/or enzyme-linked immunoelectrotransfer blot analysis are commonly used as confirmatory diagnostic tools for this disease. The most effective treatments for neurocysticercosis are tailored to individual patients that involve the use of antiepileptic drugs, analgesics, corticosteroids, and/or a combination of these. Anthelmintic drugs (albendazole) are used to treat multiple lesion neurocysticercosis. However, calcified lesions in the brain surface leading to intractable seizures and

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obstructive hydrocephalous need surgery. It is a preventable disease, accordingly, the best way to minimize the burden of this disease in underdeveloped countries such as Nepal is via (i) education of the public about the disease, (ii) providing running water supplies, (iii) developing underground sewage systems and (iv) improving personal hygiene and sanitation practices.

Introduction

Neurocysticercosis (NCC) is an infection of central nervous system by the larvae of tapeworm *Taenia solium* (*T. solium*). It is the oldest and most common helminthic infection that leads to acquired epilepsy worldwide[1]. Humans acquire taeniasis by eating raw or undercooked pork infected with cysticerci, the larval stage of *T. solium*. Transmission of cysticercosis occurs following environmental contamination with infective eggs released from the human tapeworm carrier. In developing countries, where sanitary infrastructures are often deficient, free-roaming swine acquire cysticercosis after eating human faeces containing eggs. In humans, the larval stage can also establish following accidental ingestion of eggs through eating fecal contaminated food. The disease is mostly localized to the regions where sanitation facilities such as running water supplies and underground sewage systems are lacking and hygiene (personal and otherwise) conditions are generally poor. The movement of people for better lives via immigration, migration and globalization processes has increased the spread of this disease to non-endemic regions of the world. NCC is the major health concern in the endemic areas such as Mexico, Africa, South-East Asia, Eastern Europe, and South

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America [2, 3], however the prevalence of the NCC is low in Israel, Middle-East, and most Muslim countries of Africa and Asia [4, 5]. World-wide, about 50 million people are estimated to be infected by *T. solium* and suffer from NCC and an estimated 50 thousand people die from this disease annually [6]. Further, the disease also affects unknown numbers of people from neurological burden in a productive age group [7]

Parasitic life cycle and Pathogenesis

The life cycle of *T. solium*, Figure 1, includes the swine as an intermediary host where the tapeworm develops into the larval stage. The larval stage is transmitted to humans when insufficiently cooked infected pork meat is ingested. The adult *T. solium* can be 2-8 m in length, inhabits in the small intestine and has a life-span of up to 25 years. It attaches itself to the intestinal mucosa by its double row of hooks and four suckers in the rostellum. On a regular basis as the stool passes through the intestine, 5-6 gravid proglottids (collection of fully embryonated and infective tapeworm eggs) from the distal end of the worm are passed along with the feces. Each proglottid is known to contain thousands of eggs and they are very resistant to adverse environments. In regions where open defecation is practiced and swine farming is common, the wandering swine (intermediate host) consume human feces which includes feces that may contain *T. solium* proglottids. These proglottids are emulsified by the bile and subject to proteolysis by pancreatic enzymes. These processes loosen the coatings of the proglottids and the eggs, and thousands of the oncospheres (infective embryos) are thus liberated. These

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69 oncospheres cross the intestinal wall, enter the bloodstream, and are carried to muscle,
70 other soft tissues including CNS. It takes about 60-70 days for the oncospheres develop
71 into the cysticerci. The consumption of meat containing cysticerci results in taeniasis. It
72 was previously incorrectly assumed that cysticercosis was acquired mainly through eating
73 raw/improperly cooked pork, but it is now clear that any uncooked food that may be
74 contaminated with *T. solium* eggs may also transmit (Figure 1) cysticerci. Thus, in
75 endemic areas, the disease is likely to burden all people that may be exposed to *T. solium*
76 proglottid contaminated food[8, 9]. The cysts have predilection to lodge in areas where
77 the flow of blood is high and the major parts they reside are in brain, eye and muscles.
78 The high glycogen or glucose content of these tissues (brain, muscle) may be responsible
79 for such a tropism exhibited by cysticerci [10]. When they lodge in muscle the cysts will
80 remain asymptomatic, whereas in the brain they will cause neurocysticercosis [11]. Cysts
81 are also known to reside in the heart, spinal cord and skin; however such cases are very
82 rare.

84 **Epidemiology of Cysticercosis and Neurocysticercosis in** 85 **Nepal**

86 Literature dealing with cysticercosis (epidemiological or otherwise) in Nepal is limited.
87 Efforts are made herein to summarize all available literature as well as add to that
88 knowledge by including our own data and experiences dealing with this disease in Nepal.
89 While occurrence of cysticercosis is considered as a “biological marker” of the social and

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economic development of a community[12], it is difficult to quantify the burden of neurocysticercosis in that community study. This is because of (i) its polymorphic presentation, i.e., some patients suffer only one or two episodes of seizures in the entire course of their illness while others exhibit recurrent seizures, (ii) the infection remains in latent phase throughout the life of some patients[13] and (iii) disappearance of some of the lesions in certain patients. Apart from these clinical features, social stigma associated with epilepsy forces the patients and/or their families to avoid seeking medical assistance. Additionally, some patients with other disorders, e.g., patients with syncope, migraine with aura, somatoform disorders, transient ischemic attack, focal stroke, etc., may present an acute event of seizure-like symptoms that may be interpreted or misdiagnosed as being neurocysticercosis. For example, in a recent study Devleesschauwer and associates[14] have concluded that socioeconomic status and poor personal hygiene are the major cause for the transmission of the zoonotic pork tapeworms *T. solium* and *T. asiatica*. Similarly the prevalence of taeniasis was found to be high among the *Dum* Community. This suggests that high rate of taeniasis in the certain groups might be of particular importance for maintaining the life cycle of the zoonotic swine tapeworms. This study also identified the carriers of tapeworm and determined the species to be *T. asiatica* in the endemic region of Southeast Nepal. NCC has been a common cause of epilepsy among the Nepalese soldiers[15]. Prevalence of NCC in Nepal ranges from the 0.002 to 0.1%[16], on the other hand, porcine cysticercosis was found to be 32.5 % and taeniasis ranges between to be 10-50% [17]. In 2012, the neurology service unit of Tribhuvan University teaching hospital (Kathmandu Nepal), reported 66 (36 male and 30 female) cases of

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NCC[18]. Among these 77.2% of the patients presented seizures. Computerized Tomography Scan (CT- scan) showed single ring-enhancing lesions in 42 cases (63.6%) and multiple ring enhancing lesions in the remaining 24 cases (36.3%). Most lesions were seen in parietal region (63.6%), followed by frontal (13%), temporal (9%) and occipital (9%) regions. A similar study conducted in a Kathmandu Model Hospital (n=724 patients), 61% of patients exhibited seizures and 72% of them were focal seizures due to NCC. The mean age of patients in the study was 13 years, and both sexes were found equally affected. Among these patients, 71% showed stage II lesions (dying cyst with or without edema, Table 1 and the remaining patients had stage III lesions (calcified). Overall, 61% of lesions were solitary and 31% were multiple lesions (Pant, 2006). In western region of Nepal, Basu and associates in 2007 [19] have observed that the mean age at which NCC occurs was at 10.8 years (range 11 months - 15 years, most commonly affected age group 10 - 12 years; 8.9% patients were below 2 years of age). In yet another study [20] they examined 93 patients (age range: 2-14 years; 10.3% patients <6 years of age) presenting new onset seizures from Lumbini region; 73% of the patients had NCC. These observations were confirmed by radio imaging techniques. This was further confirmed Shrestha in 2008 [21]. It is important to note that most of the epidemiological studies conducted in Nepal were at Tertiary Hospitals, they are retrospective studies and the diagnosis was based on the radio imaging techniques. Cysticercosis and NCC may also be diagnosed using immunological techniques. Immunological techniques are directed towards detecting specific proteins secreted by *T. solium* and/or specific antibodies against *T. solium* cysticerci in serum. In this regard,

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Maharjan and associates in 2002 applied an enzyme-linked immunoelectrotransfer blot (EITB) analysis technique to study cysticercosis in porcine using blood samples (n=201). The study showed 24% prevalence of cysticercosis in the tested porcine samples, 6% of them were found to be old infections or exposures. In our own study, EITB was utilized to screen for NCC using blood samples collected from patients (n= 60) that underwent CT-scanning. Most of the patients with multiple cysts showed a positive EITB test. On the other hand, among the patients with single cyst, the EITB test was positive only in a few patients. The EITB test failed to show reactive bands in the old calcified cysts. Out of 60 samples collected from patients with NCC, as suggested by CT-scan/Magnetic Resonance Imaging (MRI), EITB test was found to be positive in 18 cases. The lower percentage (30 %) of EITB positive in the samples analyzed may be due to single cyst granuloma (SCG) (Figure 2).

Clinical Characterization of Neurocysticercosis

NCC is a chronic progressive disease and the severity of the disease depends on (i) number of cysts and their location in the brain, (ii) stage of infection and intensity of host inflammatory response in the brain, and (iii) the parasite genotype[1]. In South Asian communities, including Nepal, the clinical presentation of the disease is generally considered to be solitary cysticercus granuloma as suggested by CT scans (a single ring-shaped lesion). However in some cases multiple cysts have been observed (Figure 3). In these communities, the optic cysticercosis has been rarely observed (Figure 4). Surface/cortical lesions are notorious for producing lifelong seizures due to calcification

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and subsequent scarring (Figure 5). These enhancing lesions are usually less than 20 mm in diameter and are surrounded by a varying amount of perilesional vasogenic edema. The presence of a single cyst in majority of Nepalese and/or Indian populations may be due to Toll-Like Receptor-4 (TLR4) with D299G and T399I polymorphisms. These polymorphisms are presumed to be associated with the development of symptomatic NCC via the modulation of Th1/Th2 axis[22, 23]. Similarly, depending on the location of the cysts, various neurological symptoms can occur, however they are uncommon (4-6%) in children from this region. Cysts in the midbrain are known to cause ptosis. In patients with multiple cysts in the midbrain, young children and adolescents, especially females, exhibit acute encephalitic presentation characterized by cerebral edema, and severe acute raised intracranial pressure. The most common symptom of NCC is seizures (70%-80% of the patients). These seizures are more frequent between 2nd and 5th decade of life and they are, most frequently, generalized tonic clonic seizures (GTCS) [24]. In addition to NCC, the seizures may also be caused by other factors, e.g., trauma, presence of tumor mass. Additional factors for seizures include congenital factors, infections, etc. (Figure 6). It appears that the seizures are especially common when the cysts are associated with parenchymal tissues. In a retrospective study of 250 patients visiting our hospital (Annapurna Neurological Institute and Allied Science, Kathmandu, Nepal) presenting seizures, we have found that 47.1 % of the patients had GTCS. This was followed by focal seizures secondary generalized (FSSG) in 30%, complex partial seizure (CPS) in 3.6%, atonic seizure (AS) in 2.9%, simple partial seizure (SPS) in 2.1% and drop attack (DA) in 0.7% of the patients (Figure 7).

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The asymptomatic to sudden onset of symptoms of NCC is due to the status of the cyst as well as its location. Neurological imaging techniques reveal that these cysts exist in various stages development and/or deformity, e.g., i) vesicular stage - the cyst contains live larva, ii) colloidal stage - the cyst begins to degenerate, iii) granular nodular stage - the cyst membrane thickens and calcification begins and iv) calcified stage – the cyst is fully calcified and necrotized. In patients with vesicular or colloidal stage cysts, the live larvae may elicit host immune response, and the degenerations and/or bursting of cyst results in edema which ultimately leads to seizures. Given the above, a patient may present a focal seizure (FS), FSSG, GTCS or intractable seizures. Focal neurological deficit can also occur depending on the location of lesions, e.g., diplopia in brainstem. Clinical features of raised intracranial pressure (ICP) such as headache and vomiting in cases with obstructive hydrocephalous, generalized edema in patients with multiple cysts of different stages. Blindness or visual deficit in patients with NCC can be due to intra ocular lesions (lesions along the pathway of vision). The lesions can also lead to different cognitive dysfunctions. The clinical radiological correlations of these conditions are described in in Table 1.

Radiological Diagnosis of Neurocysticercosis

The radiological diagnosis of NCC is done through imaging techniques such as CT-scanning and/or MRI. The characteristics of neuroimaging include the appearance of scolex as hyper intense nodules (hole-with-dot) as well as puncture calcification. CT is

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the best radiological method for the detection of intra-parenchymal calcifications, whereas MRI method is more suitable to resolve the differential diagnosis of NCC as it provides objective based evidences on i) the number and the topography of the lesions, ii) its stage of the involution, and iii) the degree of the inflammation. MRI is more effective in detecting extra-parenchymal NCC. One shortcoming of this technique is that it fails to detect small calcifications. In some of the cases, neither CT-scan nor MRI can detect the parasites when they are located at the subarachnoid basal cisterns[25]. Further, CT-scans of NCC and tuberculomas, pyogenic brain abscesses, mycotic granulomas, and primary and/or metastatic brain tumors often appear identical [26]. To differentiate NCC from tuberculoma and other factors such as cyst wall thickness, spontaneous disappearance of the lesion and the mid-line shift are also taken into consideration. Therefore, a more reliable techniques and/or additional diagnostic techniques for the detection of NCC are essential. One such diagnostic tool could be serological blood tests (described below). Although, CT scan and/or MRI techniques have their own technical limitations, the major limitation of the imaging techniques from the view of a patient are the accessibility and the cost associated with diagnosis for the endemic populations at risk. In poor regions of the developing world, including rural Nepal, this is not only true but a major challenge. In these regions, healthcare systems are poorly developed and the patients not only have to travel to cities for diagnosis but also cannot afford the cost associated with these tests.

Immunodiagnosics for Neurocysticercosis

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Immunodiagnosis of NCC involves the detection of proteins (antigens; Ag) secreted by *T. solium* and/or detection of circulating antibodies (Ab) against *T. solium* proteins. In fact, this would be a low cost diagnostic tool that can be effectively used for screening in the endemic areas[27]. For the detection of antibodies, either an ELISA (enzyme-linked immuno-sorbent assay) and/or EITB assays are the most commonly employed. The antibodies against *T. solium* proteins can be detected in the serum, saliva and even in the tears of patients with ophthalmic cysticercosis. Other techniques used to detect the antibodies against *T. solium* include radioimmuno assays (RIA), hemagglutination tests, complement fixation test and dipstick assay. Though ELISA is widely used to detect NCC, its sensitivity is poor. For example, its sensitivity and specificity are respectively 50% and 70% when serum samples are used for testing. On the other hand, the testing sensitivity and specificity are, respectively 87% and 95% when CSF samples used for testing. These techniques do lead to false positive tests especially when the patients are infected with *Hymenolepis nana* and *Eichhonorococcus granulosis*[28]. A comparative study of ELISA and dot-blot assay using blood samples from children with multiple brain lesions was found to be both sensitive and equally effective in diagnosis of NCC[29]. The antigen detecting ELISA tests have better sensitivity with the use of CSF specimens as compared with serum samples; however, CSF collection requires lumbar puncture. The lumbar puncture involves additional risks, the procedure is invasive and the procedure has to be performed by a trained medical professional. Given the above, this technique is not routinely practiced. It has been reported that a *T. solium* cyst fluid based lymphocyte transformation test (LTT) as a diagnostic tool for NCC is most sensitive

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(93.7%) and specific (96.2%). [30]. Even for the single cyst infection the sensitivity of this test was 87.5%. This test has future potential provided the test can be made more user friendly based on spectrophotometry.

Enzyme linked immunoelectrotransfer blot (EITB) assay:

To date, EITB is the most specific and sensitive test developed for the diagnosis of NCC by the Centers for Disease Control, Atlanta, USA. This test is considered a gold standard in serological diagnostic tests for NCC. The test detects antibodies against seven cysticerci glycoproteins. Immunoreaction with any one of the seven specific proteins is regarded as the positive test for cysticercosis (Figure 8). This assay has been used worldwide for nearly 15 years both in serological screening to determine prevalence of cysticercosis and for the diagnosis of individuals with NCC [31, 32]. It is the only assay recognized by the WHO and the Pan American Health Organization for the serological diagnosis of cysticercosis[33]. Initially, the test was considered to be 100% specific and 98% sensitive [34], however, Wilson and associates in 1991 [35] demonstrated that EITB to be only 28 % sensitive when applied to serum samples collected from patients with single cysts. In general, the serum EITB is more sensitive than that of CSF EITB. An EITB is less likely to give a positive test for cysticercosis in patients with calcified lesions as compared to those with active or transitional cysts. Further, the EITB tests may become negative after the cyst dies[36]. A demerit of the EITB test for diagnosis of NCC

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is that it can be positive in patients with taeniasis. A positive EITB test is of less diagnostic value in patients from areas where cysticercosis is endemic. Conversely, a negative EITB test does not exclude a diagnosis of NCC in patients with a single cyst or in those with brain calcifications as the only evidence of the disease. Another limitation of antibody-based tests is that the presence of antibodies may indicate only previous exposure to or infection with the parasite, and not necessarily a viable infection [37, 38]. In fact, in the scenario above, two-thirds of serologically positive individuals have no identifiable lesions on CT scans[39]. Thus, the presence of antibodies does not constitute direct evidence of a living parasite within the host[40]. For example, in Ecuador, 86% of the patients with active lesions, 67% of the patients with transitional lesions and 41% of the patients with inactive lesions were found to be positive by EITB assay with an overall sensitivity of 53.6%. In a more recently published report from the India[41], only, 26% of the patients with CT scan diagnosis of NCC were found to be positive by EITB tests. To overcome these limitations, attempts have been made to develop antigen-based assays, since detection of antigens is an indicator of the presence of live and active cysticerci[42].

Treatment

The treatment of NCC should be individualized and it should be based on the disease pathogenesis in any given patient. In this regard, the Del Brutto [43] diagnostic criteria for NCC, Table 2, is recommended. This uses a number of factors to tailor the therapy, e.g., the location of the cysts, symptoms, viability of the cysts and the degree of host

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response. In practice, the therapy for NCC is mostly directed to alleviate symptoms associated with NCC and it includes administration of antiepileptic drugs for seizures. In patients having high ICP, mannitol and oral glycerol is generally administered to reduce ICP. Corticosteroids are commonly administered to patients to reduce inflammation and edema. Albendazole in combination with either dexamethasone or prednisolone are considered for the adults and children with NCC to dissolve the cysts and reduce the incidence of seizures [44]. Improvements in treatment strategies should include the determination of the location of the cyst (e.g., intraventricular, subarachnoid or intraocular etc.) as well as use of antihelminthes drugs when the NCC patients also have HIV infection [44].

Anticysticercal drugs

Praziquantel, an isoquinolone, and albendazole, an imidazole, are the most commonly used anticysticercal drugs, especially in the treatment of intracranial cysticercosis. They are very effective in the elimination of cysticerci in the brain parenchyma and/or, at least, markedly reduce number of cysts in other locations [45]. In several comparative trials, albendazole appeared slightly more effective than praziquantel for the treatment of parenchymal NCC. Albendazole has also been found to be effective against giant parenchymal, subarachnoidal, intraventricular and even spinal forms of cysticercosis, [46]. In a double blind placebo controlled trial, 63 children with a single lesion NCC administered with albendazole (15 mg/kg/day) for a 4 week period resulted in marked

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304 reduction in the onset of seizures and faster disappearance of lesions (41% within a
305 month as compared to 16,2% in placebo patients [43]. This study also found that an 8-
306 day course of albendazole is as effective as 15 or 30 day course of albendazole treatment
307 [43]. In a randomized controlled trial from Ecuador, neither praziquintal nor albendazole
308 was found to be effective against viable cysts [47]. Similarly, in a recent randomized
309 trail from the Ecuador (n=175), it was found that only 31% patients receiving albendazole
310 were free of any active cysticerci as compared to 7% among the placebo group [48].
311 Although this variation is somewhat contradictory, it is possible that variation could be
312 due to polymorphisms associated with faster rate drug metabolism (detoxification) in the
313 host or insensitivity of cysticerci to the drugs.

314 The side effects of cysticercosis treatment with albendazole or praziquantel include
315 headache, nausea, vomiting and seizures. These effects are generally transient. The
316 transient nature of the side effects associated with albendazole or praziquantel treatment
317 seem to due to the host's inflammatory reaction to dying parasites. Corticosteroids
318 ameliorate most of the side effects listed above. Given the above, the authors' routinely
319 co-administer corticosteroids and anticysticercal therapies to their own patients in Nepal
320 as well as recommend these practices to their colleagues that treat NCC patients in Nepal
321 [[49]. Fatalities associated with the parasitic treatments are rare (1-4%) and occur
322 primarily in patients hydrocephalous, increased intracranial pressure and heavy cyst
323 burden[50]. In patients with seizures, various antiepileptics, e.g., carbamazepine,
324 phenytoin, phenobarbital and valproate have been used with roughly equal efficacy. The

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choice of drug, dose and duration of administration of antiepileptic would vary according to the clinical profile of the patients.

Surgery

Surgical intervention (Figure 9) is required in some cases particularly in intra-ventricular and subarachnoid NCC. A ventriculo peritoneal shunt is needed for hydrocephalous; simultaneous use of steroids and albendazole and recurrent courses of steroids reduce the risk of frequent obstructions and shunt revisions. Endoscopic removal of cysts is the least invasive procedure and is therefore the procedure of choice [51]–[52]. In some cases, excision of giant cysts that fail to respond to medical therapy may be required.

Prognosis

The treatments described above have excellent prognosis in case of patients with single lesions. In these cases, the seizures are usually well controlled with the first line of antiepileptic drugs, and in 60% of the cases the cysts disappear. Some patients do require prolonged antiepileptic therapy, especially when parenchymal NCC have been calcified [53]. The recurrence of the seizures is common when the multiple cysts become calcified. Cysticercus encephalitis and extra-parenchymal NCC have the guarded prognosis.

Prevention Strategy

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As per reported statistics and our on observations, most of the patients suffering from NCC come from the weaker economic sections of the society. In general they reside in villages with very poor or no sanitation systems in place. Such patients, in general, have no access to CT scan, MRI imaging facilities and/or reliable serological tests for the diagnosis of cysticercosis. These diagnostic tools are essential for the detection of the cysticerci in the brain and for the confirmation of the diagnosis. Given the above, prevention of NCC should be the priority for health systems. To prevent cysticercosis, education about health and hygiene and improvements in sanitary practices are very critical. Intervention programs to break the life cycle of parasite, e.g., porcine vaccination, anticysticercal drug treatment for the pigs infected with *T. solium*, education about proper meat cooking practices before consumption, treatment of household members if they suffer from taeniasis, etc., helps in prevention of this neglected disease[54]. Vaccination against taeniasis is not immunologically or logistically feasible at present, because the occult nature of the infection makes tapeworm carriers difficult to detect, and the minor morbidity associated with intestinal infection also makes taeniasis a poor candidate for human vaccine development[55]. Vaccinations against porcine cysticercosis are in the research phase. In the field trails, the most effective vaccination so far has been recombinant *Taenia solium* protein TSOL 18 and TSOL45-1A. The use of TSOL vaccination together with oxfendazole was effective in stopping in the transmission of *T. solium* by porcine [56].

Conclusion

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NCC the leading cause of acquired epilepsy in the developing countries including Nepal. This is a preventable disease but it is widely neglected. The realization of disease burden (cost associated with antiseizure medication, long term neurological sequel), the group of investigators have proposed to make this disease an internationally reportable disease. Better understanding of the immune response of the parasite for vaccine and drug development, and an effective intervention program is needed for the eradication of the cysticercosis in near future.

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