

1

2 **Neurocysticercosis: A Health Burden in Nepal and Other Developing**
3 **Countries.**

4 **Abstract**

5

6 Neurocysticercosis (NCC) is caused by the zoonotic parasite *Taenia solium*. In patients
7 burdened by this disease epileptic seizures are common. The disability associated with
8 this disease has been a health burden to Nepalese people. The clinical manifestations of
9 neurocysticercosis include seizures, headache, cognitive dysfunction and focal
10 neurological deficits. Computerized tomography scan (CT-scan) and Magnetic resonance
11 imaging (MRI) techniques are most commonly used investigative tools for the diagnosis
12 of NCC. Radioimaging techniques combined with serological techniques such as Enzyme
13 linked immune sorbent assay (ELISA) and/or Enzyme linked immunoelectrotransfer blot
14 (EITB) are commonly used as confirmatory diagnostic tools for this disease. The most
15 effective treatments for neurocysticercosis are tailored to individual patients that involve
16 the use of antiepileptic drugs, analgesics, corticosteroids, and/or a combination of these.
17 Anthelmintic drugs (albendazole) are used to treat multiple lesions NCC. However,
18 calcified lesions in the brain surface leading to intractable seizures and obstructive
19 hydrocephalous need surgery. It is a preventable disease; therefore, the best way to
20 minimize the burden of this disease 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*. It is the oldest and most common helminthic infection that leads to acquired epilepsy worldwide (H. H. Garcia & Del Brutto, 2005). 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 pigs 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 food². The disease is mostly localized to the regions where sanitation is poor, lack of running water supplies and underground sewage systems and poor hygiene (personal and otherwise). 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 Latin America, Asia and Africa (Bharucha, 2003; Rajshekhar, Joshi, Doanh, Van De, & Xiaonong, 2003). It is rare in Eastern and Central Europe, North America (exception - southern coast of USA) and Australia, Japan, New Zealand. On the other hand, the disease is non-existent in Israel, middle-east, and most Muslim countries of Africa and Asia (Sotelo & Del Brutto, 2002). World-wide, about 50 million people are estimated to be infected by *T. solium* and suffer

from neurocysticercosis and an estimated 50 thousand people die from this disease(Roman et al., 2000). Further, the disease also affects unknown numbers of people from neurological burden in a productive age group (White Jr, 2000)

Parasitic life cycle and Pathogenesis

The life cycle of *T. solium* (tapeworm) is depicted in Figure 1. The life cycle of *T. solium* includes the swine that are the intermediate hosts because they develop the larval stage and transmit the parasite when human beings ingest insufficiently cooked infected pork meat. The adult *T. solium* can be as long as 2-8 m in length, inhabits the human small intestine and has a life-span of up to 25 years. It attaches to the intestinal mucosa by 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 thousand liberate the oncospheres (infective embryos). These oncospheres cross the intestinal wall, enter the bloodstream, and are carried to the tissues of the host (e.g., liver, heart, lung) where embryos evolve to form larvae (also known as, cysticerci). It takes about 60-70 days before the oncospheres

develop into the cysticerci. In humans cysticerci develop when the eggs are ingested through faeco-oral contaminated food and/or consumption of improperly cooked pork meat infected with cysticerci. It was previously incorrectly assumed that cysticercosis was acquired mainly through eating raw/improperly cooked pork, but it is now clear that any uncooked food that may be contaminated with *T. solium* proglottids may transmit (Figure 1) cysticercosis. Thus, in endemic areas, the disease is likely to burden all people (vegetarians, pork consumers as well as and non-pork consumers) that may be exposed to *T. solium* proglottid contaminated food (Brown & Voge, 1985; Webbe, 1994). The cysts have predilection to lodge in areas where the flow of blood is high and the major parts they reside are in brain, eye and muscles. The high glycogen or glucose content of these tissues (brain, muscle) may be responsible for such a tropism exhibited by cysticerci (Kuruvilla, Pandian, Nair, Radhakrishnan, & Joseph, 2001). When they lodge in muscle the cysts will remain asymptomatic, whereas in the brain they will cause neurocysticercosis (Foyaca-Sibat & Del Rio-Romero, 2008). Cysts are also known to reside in the heart, spinal cord and skin; however such cases are very rare.

88 **Epidemiology of Cysticercosis and Neurocysticercosis in** 89 **Nepal**

90 Literature dealing with cysticercosis (epidemiological or otherwise) in Nepal is limited.
91 Efforts are made herein to summarize all available literature as well as add to that
92 knowledge by including our own data and experiences dealing with this disease in Nepal.
93 While cysticercosis occurrence is considered as a “biological marker” of the social and
94 economic development of a community (Pal, Carpio, & Sander, 2000), it is difficult to
95 quantify the burden of neurocysticercosis in a community study. This is because of (i) its
96 polymorphic presentation, i.e., some patients suffer only one or two episodes of seizures
97 in the entire course of their illness while others exhibit recurrent seizures, (ii) its latent
98 phase throughout infection in some patients (Fleury et al., 2003) and (iii) disappearance of
99 some of the lesions. Apart from these clinical features, social stigma associated with
100 epilepsy forces/prevents the patients or their families to seek medical assistance.
101 Additionally, some patients with other disorders, e.g., patients with syncope, migraine
102 with aura, somatoform disorders, transient ischemic attack, focal stroke, etc., may present
103 an acute event of seizure-like symptoms that may be interpreted or misdiagnosed as being
104 neurocysticercosis. For example, in a recent study Devleesschauwer and associates
105 (Devleesschauwer et al., 2012) have concluded that socioeconomic status and poor
106 personal hygiene are the major cause for the transmission of the zoonotic pork tapeworms
107 *T. solium* and *T. asiatica*.. NCC has been a common cause of epilepsy among the
108 Nepalese soldiers (Heap, 1990). Prevalence of NCC in Nepal ranges from the 0.002 to
109 0.1% (Bista, 2006), on the other hand, porcine cysticercosis was found to be 32.5 % and

110 taeniasis ranges between to be 10-50%. In 2012, the neurology service unit of Tribhuvan
 111 University teaching hospital (Kathmandu Nepal), reported 66 (36 male and 30 female)
 112 cases of neurocysticercosis(Agrawal, 2012). Among these 77.2% of the patients
 113 presented seizures. Computerized Tomography Scan (CT- scan) showed single ring-
 114 enhancing lesions in 42 cases (63.6%) and multiple ring enhancing lesions in the
 115 remaining 24 cases (36.3%). Most lesions were seen in parietal region (63.6%), followed
 116 by frontal (13%), temporal (9%) and occipital (9%) regions. A similar study conducted in
 117 a Kathmandu Model Hospital (n=724 patients), 61% of patients exhibited seizures and
 118 72% of them were focal seizures due to NCC. The mean age of patients in the study was
 119 13 years, and both sexes were found equally affected. Among these patients, 71%
 120 showed stage II lesions (dying cyst with or without edema, Table 1) and the remaining
 121 patients had stage III lesions (calcified). Overall, 61% of lesions were solitary and 31%
 122 were multiple lesions (Pant, 2006). In western Nepal, Basu and associates (2007) have
 123 observed that the mean age at which NCC occurs was at 10.8 years (range 11 months - 15
 124 years, most commonly affected age group 10 - 12 years; 8.9% patients were below 2
 125 years of age). In yet another study, (Ellis et al., 2000) further confirmed by Shrestha
 126 (2008),examined 93 patients (age range: 2-14 years; 10.3% patients <6 years of age)
 127 presenting new onset seizures from Lumbini region; 73% of the patients had NCC. These
 128 observations were confirmed by radio imaging techniques. It is important to note that
 129 most of the epidemiological studies conducted in Nepal were at Tertiary Hospitals, they
 130 are retrospective studies and the diagnosis was based on the radio imaging techniques.

131 Cysticercosis and neurocysticercosis may also be diagnosed using immunological
 132 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, Maharjan and associates (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 results, EITB was found to be sensitive in most of the patients with multiple cysts and only few sample showed positive EITB test in patients with single cyst lesions. The EITB test fails to show reactive band in the old calcified cysts. Out of 40 samples collected from patients exhibiting neurocysticercosis as suggested by CT-scan/Magnetic Resonance Imaging (MRI), EITB test was found to be positive in 18 cases. The less percentage (18%) of EITB positive in the sample analyzed may be due to single cyst granuloma (SCG) in most of the cases (Figure 2)

Clinical Characterization of Neurocysticercosis

Neurocysticercosis 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 (H. H. Garcia & Del Brutto, 2005). In south Asian communities, including Nepal and India, 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 south Asian communities, the optic cysticercosis has been rarely observed (Figure 4). Surface/cortical lesions are

157 notorious for producing lifelong seizures due to calcification and subsequent scarring
 158 (Figure 5). These enhancing lesions are usually less than 20 mm in diameter and are
 159 surrounded by a varying amount of perilesional vasogenic edema. The presence of a
 160 single cyst in majority of Nepalese and/or Indian populations may be due to Toll like
 161 receptor TLR4 D299G and T399I polymorphisms. These polymorphisms are presumed to
 162 be associated with the development of symptomatic NCC via the modulation of Th1/Th2
 163 axis (Garg & Malhotra, 2012; Verma et al., 2010). Similarly, depending on the location of
 164 the cysts, various neurological symptoms can occur, however they are uncommon (4-6%)
 165 in children from this region. Cysts in the midbrain are known to cause ptosis. In patients
 166 with multiple/numerous cysts in the midbrain, young children and adolescents, especially
 167 females, exhibit acute encephalitic presentation characterized by cerebral edema, and
 168 severe acute raised intracranial pressure. The most common symptom of NCC is seizures
 169 (70%-80% of the patients). These seizures are more frequent between 2nd and 5th decade of
 170 life and are most frequently generalized tonic clonic (O. H. del Brutto, Sotelo, & Román,
 171 1998). In addition to neurocysticercosis, the seizures may also be caused by other factors
 172 such as trauma, tumor mass, congenital factors, infections, etc. (Figure 6). It appears that
 173 the seizures are especially common when the cysts are associated with parenchymal
 174 tissues. In a retrospective study of 250 patients visiting our hospital (Annapurna
 175 Neurological Institute and Allied Science) presenting seizures, we have found that 47.1 %
 176 of the patients had generalized tonic clonic (GTCS) seizures, followed by focal seizures
 177 secondary generalized (FSSG) (30%), complex partial seizure CPS (3.6%), atonic seizure
 178 (AS) (2.9%), simple partial seizure (SPS) (2.1%) and Drop attack (DA) (0.7%) (Figure
 179 7).

The asymptomatic to sudden onset of symptoms of NCC is due to the status of the cyst as well as location of the cyst. Given the above, a patient may present a Focal seizure (FS), FSSG, GTCS or intractable seizure. Focal neurological deficit can also occur with 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 neurocysticercosis of different stages. Blindness or visual deficit can be due to intra ocular NCC or with lesions along the pathway of vision. They can also present with different cognitive dysfunction. The clinical radiological correlation is shown in Table 1.

Radiological Diagnosis of Neurocysticercosis

The radiological diagnosis of neurocysticercosis is done through imaging techniques such as CT-scanning and MRI. The characteristics of neuroimaging includes the appearance of scolex as hyper intense nodules (hole –with –dot) as well as puncture calcification. CT is the best radiological method for the detection of intraparenchymal calcification, whereas MRI is better to resolve the differential diagnosis of NCC as it provides objective based evidences on the number and the topography of the lesions, its stage of the involution and the degree of the inflammatory reaction. MRI is more effective in detecting extra-parenchymal NCC; however, 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(Wilson et al., 1991). 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 endemic populations at risk. Further, CT-scans of NCC and tuberculomas, pyogenic brain abscesses, mycotic granulomas, and primary or metastatic brain tumors often appear identical (White, 1997). Therefore, a more reliable technique or an additional diagnostic technique for the detection of NCC is essential. One such diagnostic tool could be a serological blood test.

Immunodiagnostics for Neurocysticercosis

Immunodiagnosis of neurocysticercosis involves the detection of proteins secreted by the *T. solium* (detecting antigen; Ag)/or detection of circulating antibodies (Ab) against *T. solium*. In fact, this would be a low cost diagnostic tool that can be effectively used for screening in the endemic areas (Dorny, Brandt, Zoli, & Geerts, 2003). For the detection of antibodies either an ELISA (enzyme-linked immune-sorbent assay) and/or EITB assays are the most commonly employed. The antibodies can be detected in the serum, saliva or even in the tears of patients with ophthalmic cysticercosis. Other techniques used to detect the antibodies against *T. solium* include radioimmuno assay (RIA), hemagglutination test, complement fixation test and dipstick assay. Though ELISA is widely used to detect neurocysticercosis, its sensitivity is poor. For example, its sensitivity and specificity are respectively 50% and 70% when serum is used for testing. On the other hand, the testing sensitivity and specificity are, respectively 87% and 95% when CSF is used for testing. These techniques do lead to false positive tests especially when the patients are infected with *Hymenolopsis nana* and *Eichhornia granulosis*. A comparative study of ELISA and Dot Blot assay using blood samples from children with multiple brain lesions was also found to be both were sensitive and effective in diagnosis

of NCC (Mandal, Singhi, Khandelwal, & Malla, 2006). The antigen detecting ELISA tests have better sensitivity with the use of CSF specimens as compared with serum sample, however, CSF collection requires lumbar puncture which involves certain risks and is not routinely practiced until the patients have raised intracranial pressure. It has been reported that a *T. solium* cyst fluid based lymphocyte transformation test (LTT) as a diagnostic tool for NCC is most sensitive (93.7%) and specific (96.2%). (Prasad et al., 2008). 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 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 neurocysticercosis by the Center of Disease Control, Atlanta USA. This test is considered as 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 and for diagnosis of individuals with neurocysticercosis(H. Garcia et al., 1991; V. Tsang & Wilson, 1995). It is the only assay recognized by the WHO and the Pan American Health Organization for the serological diagnosis of cysticercosis(Hancock et al., 2003). Initially, the test was considered to be 100% specific and 98% sensitive (V. C. W. Tsang, Peralta, & Ray Simons, 1983), however, Wilson and associates (1991) have shown EITB to be only 28 % of the 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 (H. H. Garcia et al., 1997). A demerit of the EITB test for diagnosis of neurocysticercosis 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 currently viable infection (García, Gilman, Tsang, & Gonzalez, 1997; Goodman, Ballagh, & Carpio, 1999). In fact, in the scenario above, two-thirds of seropositive individuals have no identifiable lesions on CT scans (Schantz, Wilkins, & Tsang, 1998). Thus, the presence of antibodies does not constitute direct evidence of a living parasite within the host (Hauser & Hesdorffer, 1990). To overcome these limitations, several attempts have been made to develop antigen-based assays, since detection of antigens revealed the presence of live and active cysticerci (Correa et al., 1999). These tests include antigen detection assays based on polyclonal and monoclonal antibodies.

In Ecuador, 86% of the patient with active lesions, 67% with transitional lesions and 41% of the patients with inactive lesions were found to be positive by EITB assay (overall sensitivity of 53.6%). In a recently published report from the South India (Rajshekhar,

Raghava, Prabhakaran, Oommen, & Muliyl, 2006), only, 26% of the patients with CT scan diagnosis of NCC were found to be positive by EITB tests.

Treatment.

The treatment of neurocysticercosis should be individualized on the basis of the pathogenesis of the disease in each patient .The proposed delbrutto(O. Del Brutto et al., 2001) diagnostic Criteria for NCC is listed in Table 2.Factors used to tailor therapy should include the location of the neurocysticercosis, symptoms, viability of the cysts and the degree of host response. Therapy in most cases is limited to the symptomatic treatment with antiepileptic drugs for seizures. In patients having high intracranial pressure, mannitol and oral glycerol is generally administered. Corticosteroids are commonly administered to patients with neurocysticercosis because of the promise that they decrease the inflammation and edema.

Anticysticercal drugs.

Praziquantel, an isoquinolone, and albendazole, an imidazole, are anticysticercal drugs that are mostly used in the treatment of intracranial cysticercosis. They mostly eliminate all the cysticerci in the brain parenchyma, or at least, markedly reduce their number(Sotelo & Jung, 1998). 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, (Takayanagui &

Jardim, 1992). In a double blind placebo controlled trial, 63 children with a single lesion NCC, were administered with albendazole (15 mg/kg/day for a 4 week) within 3 months of onset of seizures resulted in an increase in and faster disappearance of lesions (41% within a month) as compared with placebo (16.2 %) (Cruz, Cruz, Carrasco, & Horton, 1995) observed that an 8-day course of albendazole is as effective as 15 or 30 days of treatment.

In a randomized controlled trial from Ecuador, neither praziquintal nor albendazole was found to be effective for the destruction of the viable cyst (Carpio, Santillan, Leon, Flores, & Hauser, 1995). Similarly, in a recent randomized trial from the Ecuador, on 175 patients, 31% patients receiving albendazole were free of active cysts versus 7% among the placebo group (Carpio et al., 2008).

The side effects of cysticercosis treatment with albendazole or praziquantel include headache, nausea, vomiting and seizures and these effects were transient. The transient nature of the side effects associated with albendazole or praziquantel treatment seem to due to the host's inflammatory reaction to dying parasites. Corticosteroids ameliorate most of the side effects listed above. Accordingly authors have recommended routine co-administration of corticosteroids along with anticysticercal therapy (Wadia et.al 1995).

Fatalities associated with the parasitic treatments are rare (1-4%) and occur primarily in patients hydrocephalous, increased intracranial pressure and heavy cyst burden (DeGiorgio, Medina, Durón, Zee, & Escueta, 2004). In patients with seizures, various antiepileptics, e.g., carbamazepine, phenytoin, phenobarbitone and valproate have been used with roughly equal efficacy. The choice, dose, duration of antiepileptic would vary according to the clinical profile of the patients.

320

321 **Surgery**

322 Surgical intervention (Figure 9) is required in some cases particularly in intra-ventricular
323 and subarachnoid neurocysticercosis. A ventriculo peritoneal shunt is needed for
324 hydrocephalous; simultaneous use of steroids and albendazole and recurrent courses of
325 steroids reduce the risk of frequent obstructions and shunt revisions. Endoscopic removal
326 of cysts is the least invasive and is therefore the procedure of choice (Goel et al.,
327 2008)(Suri et al., 2008). Excision of giant cysts that fail to respond to medical therapy
328 may be required.

329

330

331 **Prognosis**

332 The treatments described above have excellent prognosis in case of patients with single
333 lesions. In these cases the seizures are usually well controlled with the first line of
334 antiepileptic drugs, and in 60% of the cases the cyst disappears. Some patients do require
335 prolonged antiepileptic therapy especially when parenchymal NCC have been
336 calcified(O. H. Del Brutto, 1994). The recurrence of the seizures is common when the
337 multiple cysts become calcified. Cysticercus encephalitis and extra-parenchymal NCC
338 have the guarded prognosis.

339

340

341

342

343 **Prevention Strategy**

344 Most of the patients suffering from neurocysticercosis come from the weak economic
 345 sections of the society, in general they reside in villages with very poor or no sanitation
 346 systems in place. Such patients, generally, have no access to CT scan and/or MRI
 347 imaging facilities or reliable serological tests for cysticercosis. These diagnostic tools are
 348 essential for the detection of the cysticerci in the brain and for the confirmation of the
 349 diagnosis. Given the above, prevention of NCC should be the priority for health systems.
 350 To prevent cysticercosis, education about health and hygiene and improvements in
 351 sanitary practices are very critical. Intervention programs to break the life cycle of
 352 parasite, e.g., porcine vaccination, anticysticercal drug treatment for the pigs infected
 353 with *T. solium*, education about proper cooking of the meat before consumption,
 354 treatment of household members if they suffer from taeniosis, etc., helps in prevention of
 355 this neglected disease(Budke, White, & Garcia, 2009). Vaccination against taeniasis is
 356 not immunologically or logistically feasible at present, because the occult nature of the
 357 infection makes tapeworm carriers difficult to detect, and the minor morbidity associated
 358 with intestinal infection also makes taeniasis a poor candidate for human vaccine
 359 development(Evans, 2002). Vaccinations against porcine cysticercosis are in the research
 360 phase. In the field trails, the most effective vaccination so far has been recombinant
 361 *Taenia solium* protein TSOL 18 and TSOL45-1A. The use of TSOL vaccination together
 362 with oxfendazole was effective in stopping in the transmission of *T. solium* by porcine
 363 (Lightowlers, 2010).

364

Conclusion

Neurocysticercosis is 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 antiepileptic medication, long term neurological sequelae), 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.

Acknowledgement.

We are very much thankful to Dr. Patricia Wilkins, Center for Disease Control (CDC, USA) for Providing the EITB strips and guidance for conducting the research work. I am thankful to Mr. Subodh Kant Singh, Ms. Mandira Dahal and Kumar Basnet for providing data for preparing the manuscript.

386 References

- 387 Agrawal, J. (2012). Neurocysticercosis in Nepal and It's Global Perspective. *Kathmandu*
388 *University Medical Journal*, 9(2), 1-2.
- 389 Bharucha, N. (2003). Epidemiology of epilepsy in India. *Epilepsia*, 44, 9-11.
- 390 Bista, M. (2006). Epidemiology, prevention and control of human cysticercosis/taeniasis
391 in Nepal. *Proceedings of present situation challenges in treatment and*
392 *elimination of Taeniasis/cysticercosis in Nepal*, edited by Joshi DD, Sharma M,
393 Rana S. National Zoonoses & Food Hygeine Research Centre, Kathmandu, 12-
394 14.
- 395 Brown, W., & Voge, M. (1985). Cysticercosis. A modern day plague. *Pediatric Clinics of*
396 *North America*, 32(4), 953.
- 397 Budke, C. M., White, A. C., & Garcia, H. H. (2009). Zoonotic larval cestode infections:
398 neglected, neglected tropical diseases? *PLoS neglected tropical diseases*, 3(2),
399 e319.
- 400 Carpio, A., Kelvin, E. A., Bagiella, E., Leslie, D., Leon, P., Andrews, H., & Hauser, W.
401 A. (2008). Effects of albendazole treatment on neurocysticercosis: a randomised
402 controlled trial. *Journal of Neurology, Neurosurgery & Psychiatry*, 79(9), 1050-
403 1055.
- 404 Carpio, A., Santillan, F., Leon, P., Flores, C., & Hauser, W. A. (1995). Is the course of
405 neurocysticercosis modified by treatment with antihelminthic agents? *Archives of*
406 *internal medicine*, 155(18), 1982.
- 407 Correa, D., Sarti, E., Tapia-Romero, R., Rico, R., Alcántara-Anguiano, I., Salgado, A., . .
408 . Flisser, A. (1999). Antigens and antibodies in sera from human cases of epilepsy
409 or taeniasis from an area of Mexico where *Taenia solium* cysticercosis is
410 endemic. *Annals of Tropical Medicine and Parasitology*, 93(1), 69-74.
- 411 Cruz, I., Cruz, M., Carrasco, F., & Horton, J. (1995). Neurocysticercosis: optimal dose
412 treatment with albendazole. *Journal of the Neurological Sciences*, 133(1), 152-
413 154.
- 414 DeGiorgio, C. M., Medina, M. T., Durón, R., Zee, C., & Escueta, S. P. (2004).
415 Neurocysticercosis. *Epilepsy Currents*, 4(3), 107-111.
- 416 Del Brutto, O., Rajshekhar, V., White Jr, A., Tsang, V., Nash, T., Takayanagui, O., . . .
417 Correa, D. (2001). Proposed diagnostic criteria for neurocysticercosis. *Neurology*,
418 57(2), 177-183.
- 419 Del Brutto, O. H. (1994). Prognostic factors for seizure recurrence after withdrawal of
420 antiepileptic drugs in patients with neurocysticercosis. *Neurology*, 44(9), 1706-
421 1706.
- 422 del Brutto, O. H., Sotelo, J., & Román, G. C. (1998). *Neurocysticercosis*: Garland
423 Science.
- 424 Devleesschauwer, B., Aryal, A., Joshi, D. D., Rijal, S., Sherchand, J. B., Praet, N., . . .
425 Dorny, P. (2012). Epidemiology of *Taenia solium* in Nepal: is it influenced by the
426 social characteristics of the population and the presence of *Taenia asiatica*?
427 *Tropical Medicine & International Health*.
- 428 Dorny, P., Brandt, J., Zoli, A., & Geerts, S. (2003). Immunodiagnostic tools for human
429 and porcine cysticercosis. *Acta Tropica*, 87(1), 79-86.

- 430 Ellis, M., Manandhar, D., Manandhar, N., Wyatt, J., Bolam, A., & de LCostello, A.
431 (2000). Stillbirths and neonatal encephalopathy in Kathmandu, Nepal: an estimate
432 of the contribution of birth asphyxia to perinatal mortality in a low-income urban
433 population. *Paediatric and perinatal epidemiology*, 14(1), 39-52.
- 434 Evans, C. A. W. (2002). 42 Taenia solium Vaccination: Present Status and Future
435 Prospects. *Taenia solium cysticercosis: from basic to clinical science*, 421.
- 436 Fleury, A., Gomez, T., Alvarez, I., Meza, D., Huerta, M., Chavarria, A., . . . Preux, P.
437 (2003). High prevalence of calcified silent neurocysticercosis in a rural village of
438 Mexico. *Neuroepidemiology*, 22(2), 139-145.
- 439 Foyaca-Sibat, H., & Del Rio-Romero, I. (2008). Prevalence Of Epilepsy In An Endemic
440 Area For Neurocysticercosis In South Africa. *The Internet Journal of Neurology*,
441 9(1).
- 442 Garcia, H., Herrera, G., Diaz, F., Verastegui, M., Gallo, C., Naranjo, J., . . . Alvarado, M.
443 (1991). Diagnosis of cysticercosis in endemic regions. *The Lancet*, 338(8766),
444 549-551.
- 445 Garcia, H. H., & Del Brutto, O. H. (2005). Neurocysticercosis: updated concepts about an
446 old disease. *The Lancet Neurology*, 4(10), 653-661.
- 447 Garcia, H. H., Gilman, R. H., Catacora, M., Verastegui, M., Gonzalez, A. E., & Tsang, V.
448 C. W. (1997). Serologic evolution of neurocysticercosis patients after antiparasitic
449 therapy. *Journal of Infectious Diseases*, 175(2), 486.
- 450 García, H. H., Gilman, R. H., Tsang, V. C. W., & Gonzalez, A. E. (1997). Clinical
451 significance of neurocysticercosis in endemic villages. *Transactions of the Royal*
452 *Society of Tropical Medicine and Hygiene*, 91(2), 176-178.
- 453 Garg, R. K., & Malhotra, H. S. (2012). Solitary cysticercus granuloma. *Expert Review of*
454 *Anti-infective Therapy*, 10(5), 597-612.
- 455 Goel, R. K., Ahmad, F. U., Vellimana, A. K., Suri, A., Chandra, P. S., Kumar, R., . . .
456 Mahapatra, A. K. (2008). Endoscopic management of intraventricular
457 neurocysticercosis. *Journal of Clinical Neuroscience*, 15(10), 1096-1101.
- 458 Goodman, K. A., Ballagh, S. A., & Carpio, A. (1999). Case-control study of
459 seropositivity for cysticercosis in Cuenca, Ecuador. *The American journal of*
460 *tropical medicine and hygiene*, 60(1), 70-74.
- 461 Hancock, K., Khan, A., Williams, F. B., Yushak, M. L., Patabhi, S., Noh, J., & Tsang, V.
462 C. W. (2003). Characterization of the 8-kilodalton antigens of Taenia solium
463 metacestodes and evaluation of their use in an enzyme-linked immunosorbent
464 assay for serodiagnosis. *Journal of Clinical Microbiology*, 41(6), 2577-2586.
- 465 Hauser, W. A., & Hesdorffer, D. C. (1990). *Epilepsy: frequency, causes, and*
466 *consequences*: Epilepsy Foundation of America Landover, MD.
- 467 Heap, B. (1990). Cerebral cysticercosis as a common cause of epilepsy in Gurkhas in
468 Hong Kong. *Journal of the Royal Army Medical Corps*, 136(3), 146-149.
- 469 Kuruvilla, A., Pandian, J., Nair, M., Radhakrishnan, V., & Joseph, S. (2001).
470 Neurocysticercosis: a clinical and radiological appraisal from Kerala State, South
471 India. *Singapore medical journal*, 42(7), 297-303.
- 472 Lightowlers, M. W. (2010). Eradication of Taenia solium cysticercosis: a role for
473 vaccination of pigs. *International Journal for Parasitology*, 40(10), 1183-1192.
- 474 Mandal, J., Singhi, P., Khandelwal, N., & Malla, N. (2006). Evaluation of ELISA and dot
475 blots for the serodiagnosis of neurocysticercosis, in children found to have single

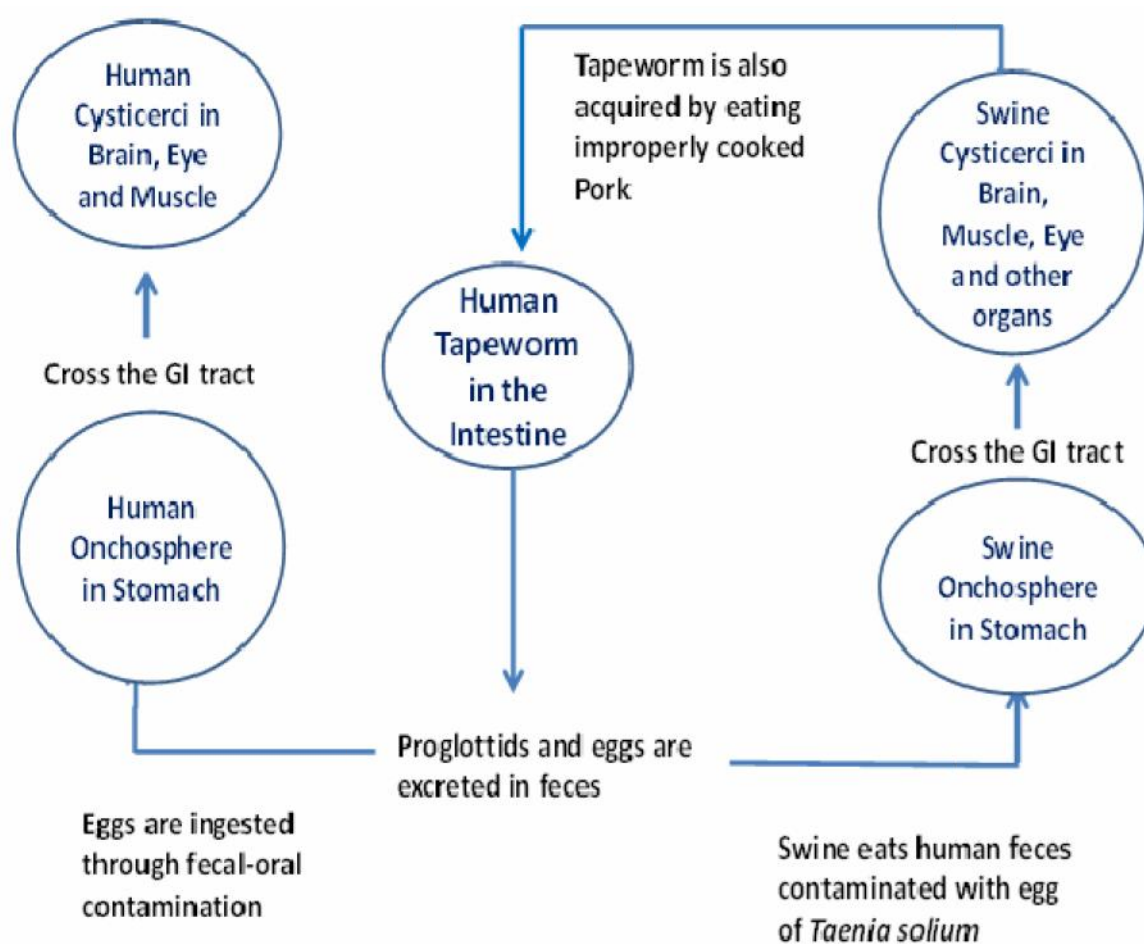
- 476 or multiple enhancing lesions in computerized tomographic scans of the brain.
477 *Annals of tropical medicine and parasitology*, 100(1), 39-48.
- 478 Pal, D. K., Carpio, A., & Sander, J. W. A. S. (2000). Neurocysticercosis and epilepsy in
479 developing countries. *Journal of Neurology, Neurosurgery & Psychiatry*, 68(2),
480 137-143.
- 481 Prasad, A., Prasad, K. N., Yadav, A., Gupta, R. K., Pradhan, S., Jha, S., . . . Husain, M.
482 (2008). Lymphocyte transformation test: a new method for diagnosis of
483 neurocysticercosis. *Diagnostic Microbiology and Infectious Disease*, 61(2), 198-
484 202.
- 485 Rajshekhar, V., Joshi, D. D., Doanh, N. Q., Van De, N., & Xiaonong, Z. (2003). Taenia
486 solium taeniosis/cysticercosis in Asia: epidemiology, impact and issues. *Acta*
487 *Tropica*, 87(1), 53-60.
- 488 Rajshekhar, V., Raghava, M. V., Prabhakaran, V., Oommen, A., & Muliyl, J. (2006).
489 Active epilepsy as an index of burden of neurocysticercosis in Vellore district,
490 India. *Neurology*, 67(12), 2135-2139.
- 491 Roman, G., Sotelo, J., Del Brutto, O., Flisser, A., Dumas, M., Wadia, N., . . . Bittencourt,
492 P. R. M. (2000). A proposal to declare neurocysticercosis an international
493 reportable disease. *Bulletin of the world Health Organization*, 78(3), 399-406.
- 494 Schantz, P. M., Wilkins, P. P., & Tsang, V. C. W. (1998). Immigrants, imaging, and
495 immunoblots: the emergence of neurocysticercosis as a significant public health
496 problem. *Emerging infections*, 213-242.
- 497 Sotelo, J., & Del Brutto, O. H. (2002). Review of neurocysticercosis. *Neurosurgical*
498 *Focus*, 12(6), 1-7.
- 499 Sotelo, J., & Jung, H. (1998). Pharmacokinetic optimisation of the treatment of
500 neurocysticercosis. *Clinical pharmacokinetics*, 34(6), 503-515.
- 501 Suri, A., Goel, R. K., Ahmad, F. U., Vellimana, A. K., Sharma, B. S., & Mahapatra, A.
502 K. (2008). Transventricular, transaqueductal scope-in-scope endoscopic excision
503 of fourth ventricular neurocysticercosis: a series of 13 cases and a review.
- 504 Takayanagui, O. M., & Jardim, E. (1992). Therapy for neurocysticercosis: comparison
505 between albendazole and praziquantel. *Archives of neurology*, 49(3), 290.
- 506 Tsang, V., & Wilson, M. (1995). Taenia solium cysticercosis: An under-recognized but
507 serious publica health problem. *Parasitology Today*, 11(3), 124-126.
- 508 Tsang, V. C. W., Peralta, J. M., & Ray Simons, A. (1983). [29] Enzyme-linked
509 immunoelectrotransfer blot techniques (EITB) for studying the specificities of
510 antigens and antibodies separated by gel electrophoresis. *Methods in Enzymology*,
511 92, 377-391.
- 512 Verma, A., Prasad, K. N., Gupta, R. K., Singh, A. K., Nyati, K. K., Rizwan, A., . . .
513 Paliwal, V. K. (2010). Toll-like receptor 4 polymorphism and its association with
514 symptomatic neurocysticercosis. *Journal of Infectious Diseases*, 202(8), 1219.
- 515 Webbe, G. (1994). Human cysticercosis: parasitology, pathology, clinical manifestations
516 and available treatment. *Pharmacology & Therapeutics*, 64(1), 175-200.
- 517 White, A. C. (1997). Neurocysticercosis: a major cause of neurological disease
518 worldwide. *Clinical Infectious Diseases*, 24(2), 101-113.
- 519 White Jr, A. C. (2000). Neurocysticercosis: updates on epidemiology, pathogenesis,
520 diagnosis, and management. *Annual Review of Medicine*, 51(1), 187-206.

521 Wilson, M., Bryan, R. T., Fried, J. A., Ware, D. A., Schantz, P. M., Pilcher, J. B., &
 522 Tsang, V. C. W. (1991). Clinical evaluation of the cysticercosis enzyme-linked
 523 immunoelectrotransfer blot in patients with neurocysticercosis. *Journal of*
 524 *Infectious Diseases*, 164(5), 1007-1009.

527

528 **Figure 1: Schematic Representation of Life Cycle of *TaeniaSolium***

529



530

531

532

533

534

535

536

537

538

539

540

541

542

543

544

545

546

547

548

549

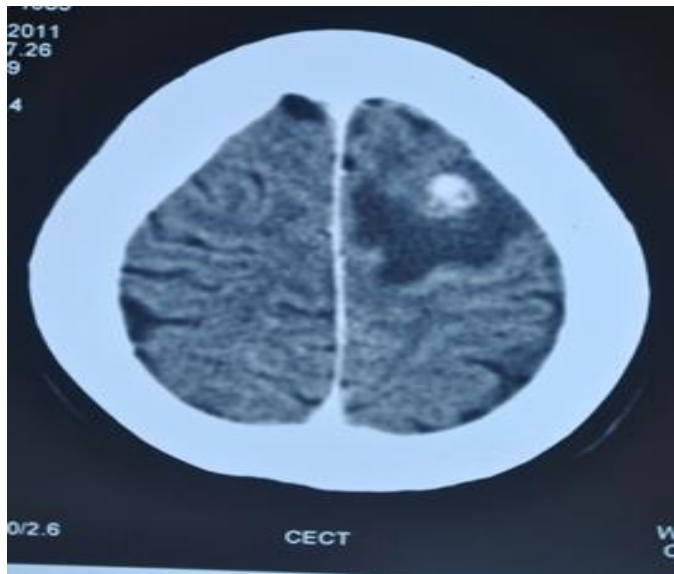
550

551

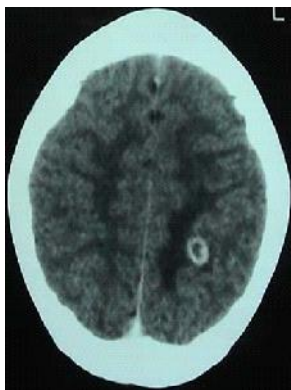
552

553 **Figure 2: Schematic representation of Single cyst with edema**
554 **presents the brain.**

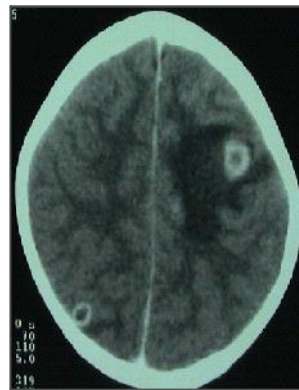




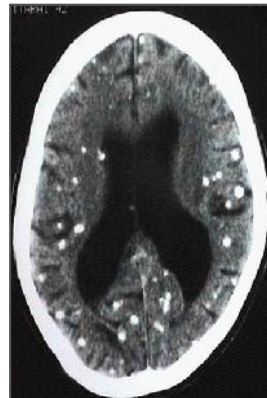
Lesions seen in NCC



Solitary



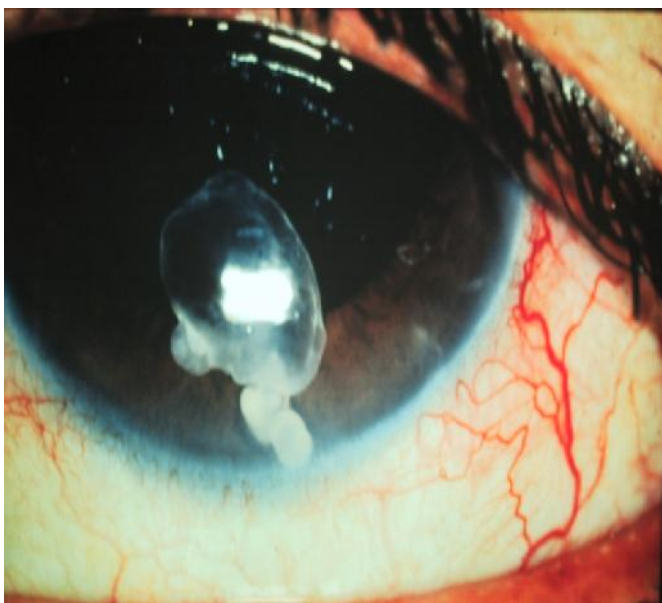
Few



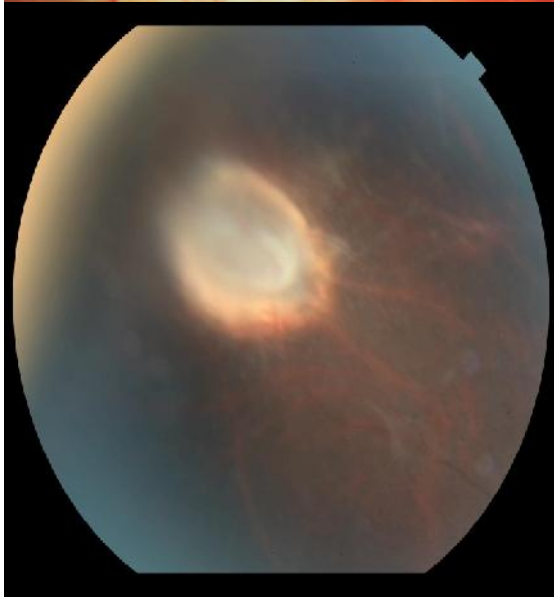
Multiple

556 **Figure 3 - CT-Scans showing of single, few and multiple cysts, respectively.**

557



558



559

560 **Figure 4: Optic Cysticercosis.**

561



Figure 5: CT- Scan of Calcified Surface lesion.

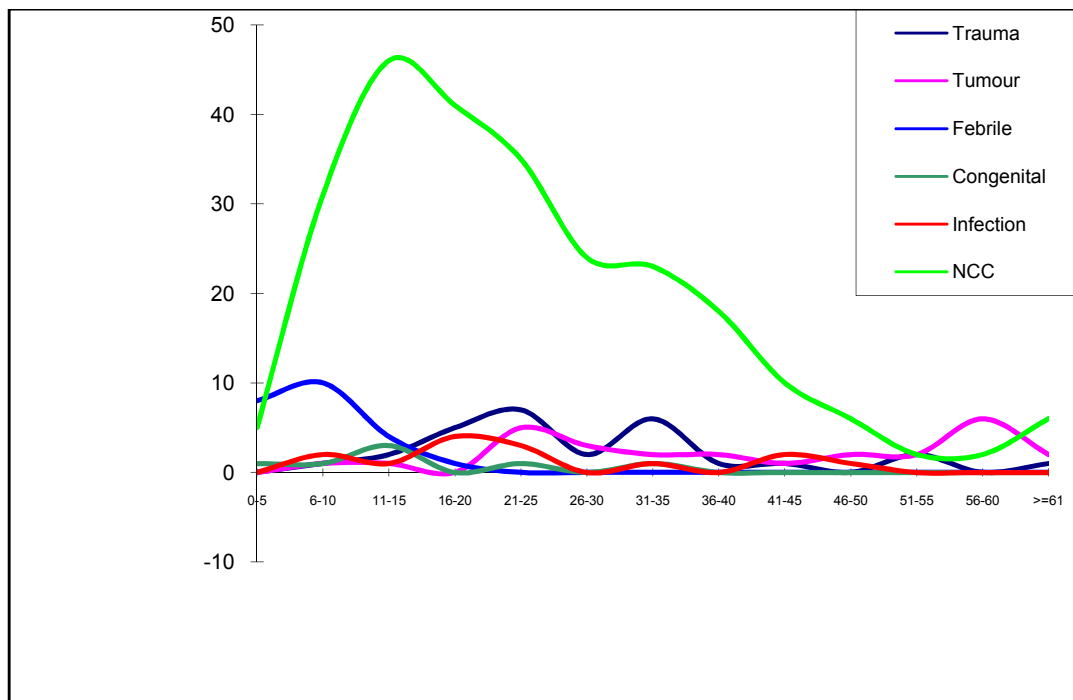
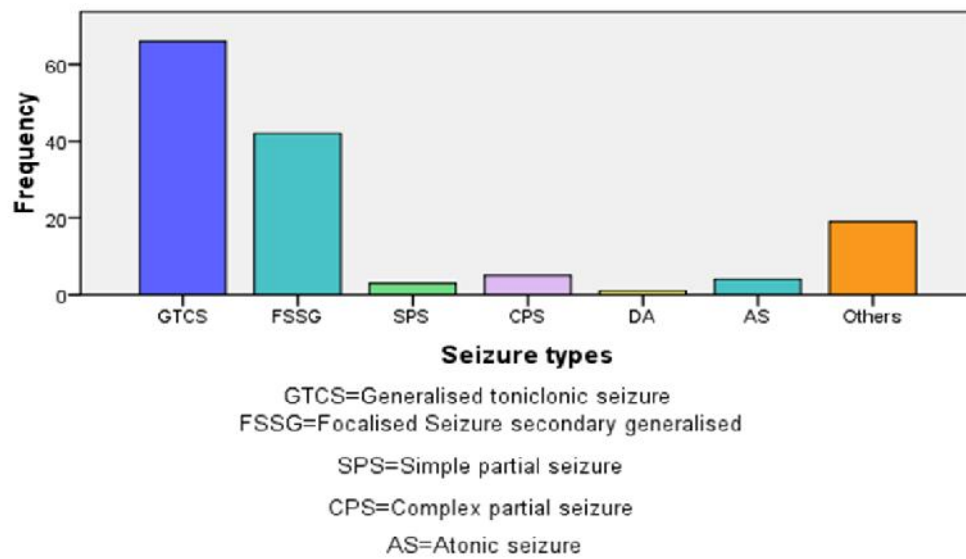


Figure 6: Occurrence of seizure in humans with age and factors that influence occurrence of seizures.



569

570 Figure 7: Frequency of different type of Seizure in humans among different age groups.

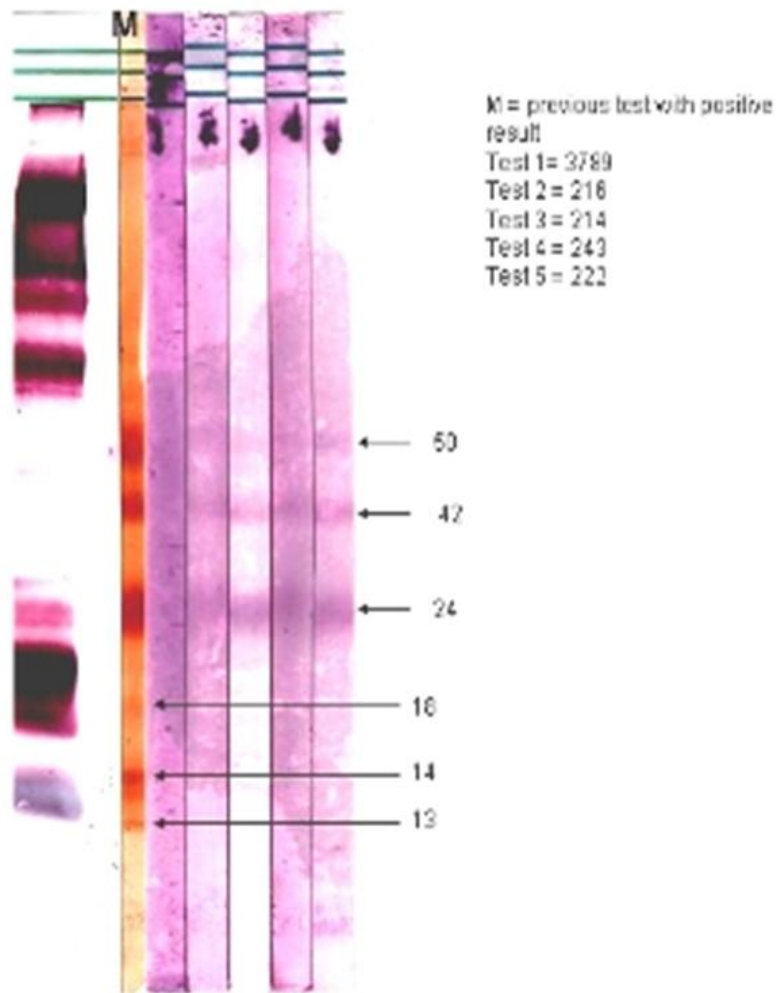


Figure 8: Enzyme linked immunoelectro transfer blot (EITB) assay showing three specific antigenic bands of 50, 42 and 24 KDa. M-marker and test 1, 2, 3 4, 5 represents the test sample which is diagnoses Neurocysticercosis (imaging findings). Lane 1 shows no reactive bands.



Cyst in 4th Ventricle Pipette suction of cyst

577

578 Figure 9: Surgical removal (pipette suction method) of Cyst present in 4th ventricle

579

580

581

582

583

584

585

586

587

588

589

590

591

592 Table 1: Radiological appearance of cysts and symptoms associated with the status of
593 cyst.

594

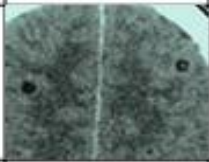
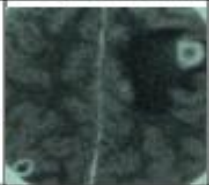
Stage	Status of cyst	Radiological appearance	Symptoms	Imaging
I	Living	Hypodense	Incidental	
II	Dying	Ring or disc enhancing lesion with edema (IIE+), Without edema (IIE-)	Seizure Focal ND Rarely ICP	
III	Dead	Hyperdense lesion No enhancement with edema (IIIE+), Without edema (IIIE-)	None or Seizure	

Table 2 –Guidelines for Treatment of Neurocysticercosis

Parenchymal neurocysticercosis		Treatment strategy
Viable cysts		Cysticidal treatment + steroids
Calcified		AED; No cysticidal therapy
Enhancing lesions		
Single		AED; Cysticidal drugs if persistent
Multiple		Anticonvulsant + cysticidal and steroids
Extraparenchymal neurocysticercosis		
Intraventricular cyst		Neuroendoscopic removal
Subarachnoid cyst		Cysticidal treatment + steroids
Spinal cysticercosis		
		Cysticidal treatment + steroids