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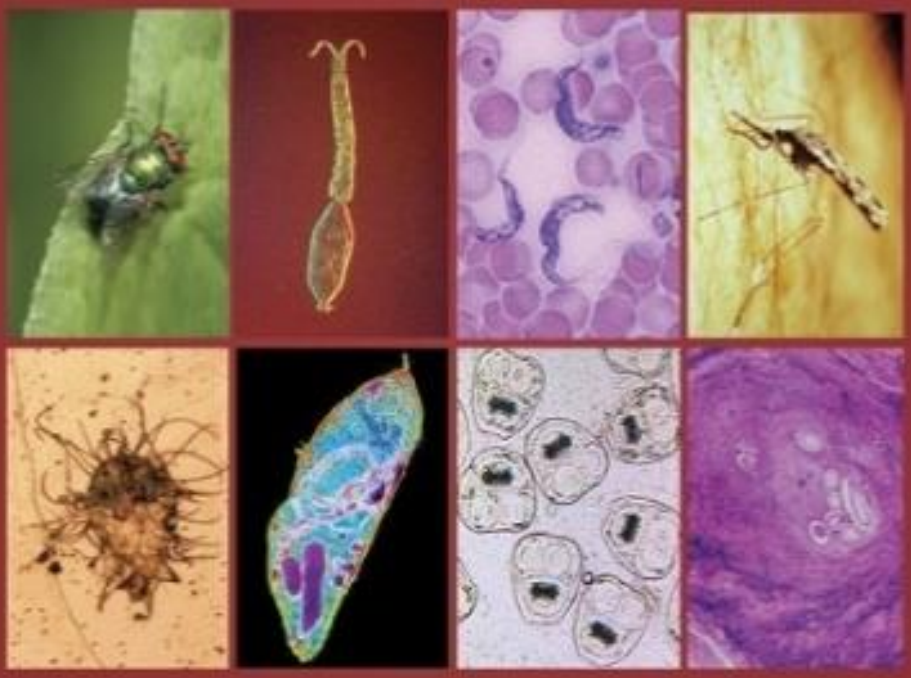

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A Neglected Dangerous Parasitic Disease Overview: Neurocysticercosis

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ABSTRACT

The furthermost widespread helminthic disease of the central nervous system globally, neurocysticercosis (NCC) is an infection of the central nervous system as well as meninges through *Taenia solium* larvae. This disease's pleomorphism is caused by pathological alterations caused by the lodgment of parasites in the brain's parenchyma, subarachnoid space, ventricular system, otherwise spinal cord. Overall, epilepsy, increased intracranial pressure, headache, and focal impairments are the most common clinical manifestations. After analyzing clinical data, neuroimaging study results, and immunological test results, an accurate diagnosis of NCC can be made. Neuroimaging methods, however, remain crucial for diagnosis as clinical findings and immunological results only offer suggestive evidence of NCC. Once cysticidal medications were available, most NCC patients had a different prognosis. According to numerous patient reports, these medications can lessen the infection in addition to enhancing clinical improvement. Control efforts against the *T. solium* life stages, including pigs harboring the adult stage, sick pigs, and eggs in the environment, should be implemented in an effort to completely eradicate the illness.

INTRODUCTION

The most prevalent helminthic illness attacking the central nervous system in humans is neurocysticercosis (Garcia, 2021). A pig sickness was its definition in ancient Greece. The disease is broadly spread in the developing regions which have a warm environment as well as extreme poverty that facilitate the spread of this parasitosis. The incidence of epilepsy in developed countries, and rural villages of endemic ones revealed that the primary cause of epilepsy observed in these locations is neurocysticercosis (Ndimubanzi *et al.*, 2010).

A leading cause of admissions to neurological hospitals in the urban areas of developing nations is neurocysticercosis, where the illness also poses a health risk (Coyle, 2014). The frequency of neurocysticercosis patients in the industrialized world has recently increased, coinciding with an increase in immigration from endemic countries. According to Bruno *et al.* (2013), immigrants from Latin America account for over 90% of American and European people with neurocysticercosis.

Although most cases of neurocysticercosis are acquired via a contact at home that has an adult *Taenia solium* in its intestinal tract, the disease has also been identified in individuals who have never traveled to endemic places (Hunter *et al.*, 2018). Neurocysticercosis is an interesting disease because of the host's unanticipated immunological reaction toward cysticerci, as well as the pleomorphic damage these parasites induce within the brain and nervous system (Coyle, 2019).

2. What causes Neurocysticercosis?

Two hosts are involved in *Taenia solium*'s intricate life cycle. Humans are the only beings that serve as definitive hosts for the mature tapeworm; however, both humans and pigs can act as intermediate hosts for the cysticercus larvae. Throughout the typical transmission cycle, fully developed *T. solium* dwells in its host's small intestine. By powerful suckers along with hooks, it is fastened into the intestinal mucosa. Gravid segments, which are cut off from a worm's posterior end, are passed along with the excrement, releasing thousands of fertile eggs into the environment (Lescano *et al.,* 2019).

When human waste is not properly disposed of, pigs are fed human waste that contains *T. solium* eggs. After the eggs present inside the pig's digestive tract shedding their coverings and releasing oncospheres, they penetrate the stomach wall and enter the bloodstream. After there, they enter the tissues where they transform into cysticerci. When a human consumes incorrectly cooked pork meat, cysticerci can be released into the small intestine, the digestive enzymes acting on its scolices causing them to evaginate and stick to the wall of the intestine. Proglottids start to multiply as soon as the scolex attaches, and they will reach maturity four months after infection. After consuming its eggs, humans can also serve as *T. solium*'s intermediate hosts. Human cysticercosis arises under various conditions. Humans can contract cysticercosis by either eating food tainted with the parasite ova or by fecal-oral infection from those who have adult parasites living within their intestines. Current epidemiological research has refuted earlier theories that attributed human infection with *T. solium* eggs to the environment by demonstrating Individuals suffering from cysticercosis congregating close to taeniasic people (Garcia and Del Brutto, 2020).

The two main primary components of cysticerci are both the vesicular wall as well as the scolex. Cysticerci are at a vesicular “viable” stage (Fig. 1) subsequently entering the nervous system. During this stage, cysticerci feature a transparent membrane, and clear fluid, in addition to a typical invaginated scolex, that are able to survive for a long time (Del Brutto, 2012).

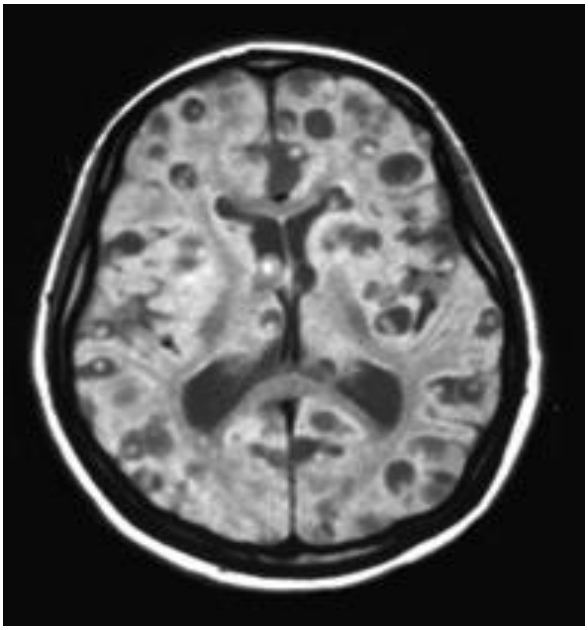

Fig. 1. MRI reveals multiple intraparenchymal viable cysticerci with scolex. Quoted from “Takayanagui and Haes, 2022”.

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Because of the host's immunological response, they begin a degenerative process that terminates in their conversion into calcifications. In the colloidal stage **(Fig. 2),** which is the initial stage of cysticerci involution, the scolex is distinguished by hyaline degeneration and unclear vesicular fluid. Following this stage, there is a thickness in the cyst wall as well as the turn of the scolex into mineralized granules, and cysticerci is no longer viable which is known as the granular stage. In the end, the parasite residues manifest as a calcified stage (Fig. 3), or mineralized nodule (Wen *et al.,* 2019).

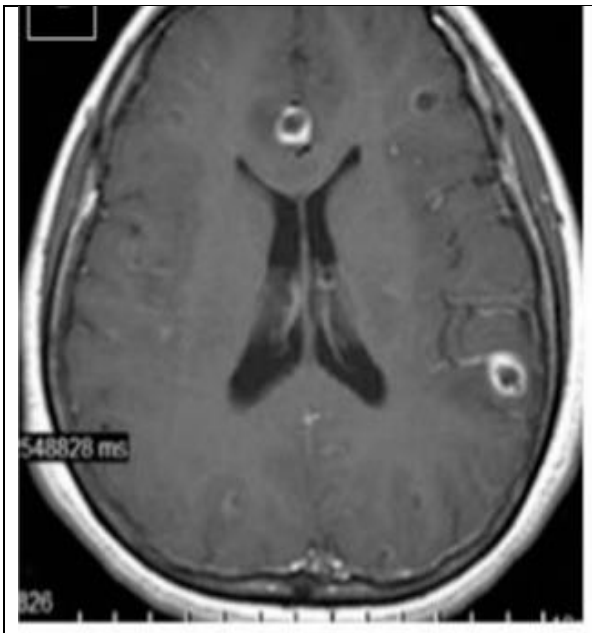

Fig. 2. Colloidal cysticerci that present as ring-enhancing lesions on an MRI. Taken from "Del Brutto et al., 2022".

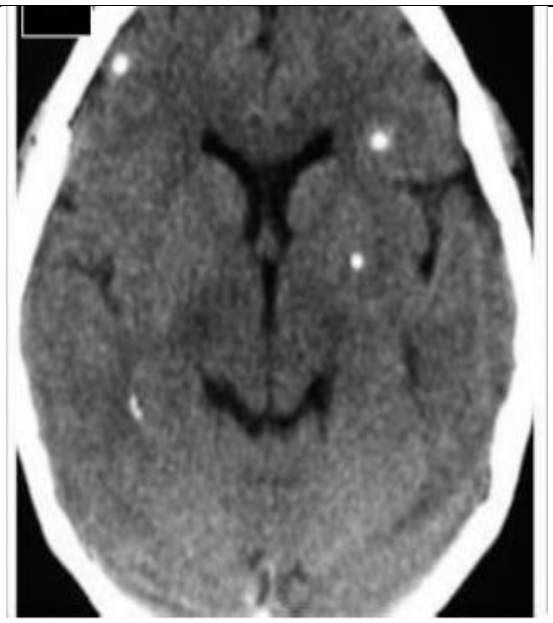

Fig. 3. Non-enhanced CT scan Parenchymal brain calcifications. Del Brutto et al., 2022 is used as a source.

The surrounding tissue evokes a mild inflammatory reaction to vesicular cysticerci (Carmen-Orozco et al., 2019). On the other hand, colloidal cysticerci frequently include a collagen-like coat and a cellular inflammatory response that contains the worm within. The parenchyma surrounding the brain is seen to have perivascular lymphocyte cuffing, astrocyte gliosis, proliferating microglia, edematous swelling and degenerative changes in the neurons. These edematous swelling decreases but the astrocytic alterations around the lesions may intensify, and epithelioid cells begin to develop and merge to create multinucleated giant cells as the parasites reach the granular and calcified stages. Typically, meningeal cysticerci cause a significant inflammatory response in the subarachnoid space, resulting in the production of an exudate that abnormally thickens the leptomeninges and is made up of lymphocytic, eosinophilic and multinucleated cells, fibers of collagen as well as the hyalinized membrane of the parasite (Mahale *et al.*, 2015).

The cranial and optic nerves that emerge from the brainstem, and tiny penetrating arteries that emerge from the circle of Willis may all sustain damage as a result of this widespread inflammation, which could obstruct the vessel's lumen and cause a cerebral infarction (Garcia *et al.,* 2014). Thickened leptomeninges and parasite membranes can additionally block the foramina of Luschka and Magendie, leading to obstructive hydrocephalus development. If ventricular cysticerci are

affixed to the choroid neural plexus or the wall of the ventricle, they may also cause an inflammatory response. When the ependymal lining disruption is in proximity to both the foramina of Monro as well as the cerebral aqueduct, it can extend towards these ventricular cavities, obstructing CSF transport (Takayanagui and Haes, 2022).

While some cysticercal antigens particularly antigen B evade the immune surveillance against cysticerci, others promote the development of certain antibodies that serve as the foundation for the immunological cysticercosis detection (Wen et al., 2019). Furthermore, cellular immunological dysfunction has been proposed as a possible outcome of reduced lymphocyte proliferation, inappropriate cytokine concentrations, and elevated subpopulations of CD8 T-lymphocytes in neurocysticercosis patients. The hypothesis suggests that the observed correlation between neurocysticercosis and immunodeficiency states, as well as the occurrence of gliomas, could be caused by this weakened cellular immunity. Within these scenarios, the parasites which are surrounded by high glial proliferation and the weakened cellular immune responses could potentially hinder the immune system's ability to detect cancer, ultimately resulting in the malignant transformation of astrocytes (Prodjinotho *et al.,* 2020).

3. Clinical Signs and Symptoms:

Individual disparities in the quantity and location of CNS lesions as well as variances in the intensity of disease activity are linked to the neurocysticercosis clinical pleomorphism. The most prevalent clinical symptom of neurocysticercosis is seizures, which may be the main or only symptom of the illness in about 70% of cases (Garcia *et al.,* 2020).

According to Nash *et al.* (2015), a prominent contributing factor in acquired epilepsy is neurocysticercosis. Seizures are more likely to occur in the parenchymal type of neurocysticercosis compared with subarachnoid and ventricular types (Del Brutto *et al.,* 2016). There has been a discussion on how persons with calcified neurocysticercosis exhibit epileptogenesis. A process of calcification remodeling may expose parasite antigens which are trapped in the calcium matrix to the immune system of the host, causing recurrent seizures. Although calcifications have historically been thought of as inactive lesions, recent research suggests that calcified cysticerci are not clinically or pathologically inactive lesions (Herric *et al.,* 2018).

According to Ghasemi *et al.* (2016), up to 20% of neurocysticercosis patients exhibit focal neurological symptoms that change based on the parasites' size, quantity, and location. Involuntary movements, Parkinsonian rigidity, sensory deficiencies, language disorders, and brainstem dysfunction symptoms can occur in certain patients, but indicators of pyramidal tract dysfunction predominate. Primarily seen among those who have large sub-arachnoid cysts squeezing the parenchyma of the brain, these manifestations typically are transient or persistent in nature similar to that of brain tumors (Fig. 4). Stroke symptoms are also reported in approximately 3% of individuals with neurocysticercosis; these are primarily associated with cerebral infarctions in the brainstem, corona radiata, or the internal capsule. Neurocysticercosis individuals may experience focal neurological symptoms or seizures in addition to intracranial hypertension. As to Fleury *et al.* (2011), hydrocephalus is the most frequent cause of this syndrome and can be attributed to ventricular cysts, granular ependymitis, or cysticercotic arachnoiditis.

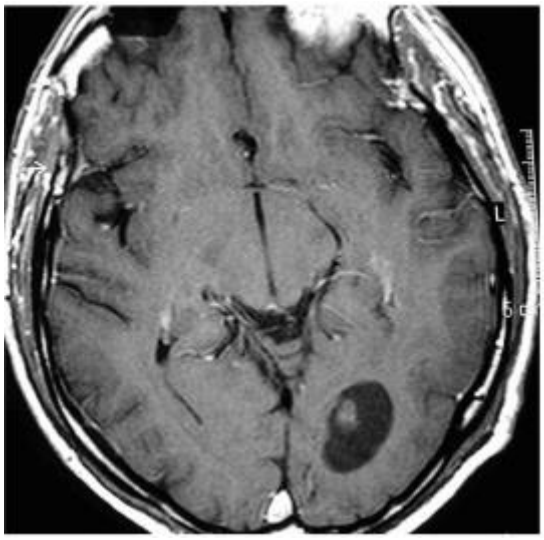

Fig. 4. Scolex mimics in a patient with adenocarcinoma and brain metastasis. Quoted from "Del Brutto *et al.,* 2017".

Cysticercotic encephalitis patients, a serious form of neurocysticercosis induced by a vast parenchymal cysticerci infection inciting a significant host immunological response, also have intracranial hypertension. This illness, which is more common in children as well as young females, is distinguished by headache, vomiting, papilledema, epileptic attacks, clouding of consciousness, and a decrease in the acuity of vision. Some patients with neurocysticercosis may exhibit psychiatric symptoms, which can vary from severe dementia to subpar performance on neuropsychological testing. A few of these patients spent years in psychiatric institutes before an autopsy revealed an accurate diagnosis (Nau *et al.,* 2018).

4. Assessment:

Many patients still struggle with the diagnosis of neurocysticercosis, despite advancements in immunological testing and neuroimaging. Nonspecific clinical symptoms, non-pathognomonic neuroimaging findings, and issues with relatively low specificity and sensitivity with serologic testing are all present (Goyal et al., 2020; Guzman and Garcia, 2021).

4.1. CT and MRI Neuroimaging Tests:

Offer unbiased proof regarding the quantity, shape, and involutional stage of the lesions (Kimura-Hayama *et al.,* 2010). Compact, spherical cysts which may clearly distinguished from the brain parenchyma around them on CT as well as MRI images are the hallmarks of vesicular cysticerci. Convolutional augmentation and edema are absent. Accompanying a pathognomonic "hole-with-dot" look (Fig. 5), many of these lesions contain an eccentric hyperdense nodule inside that represents the scolex (Venkat *et al.,* 2016).

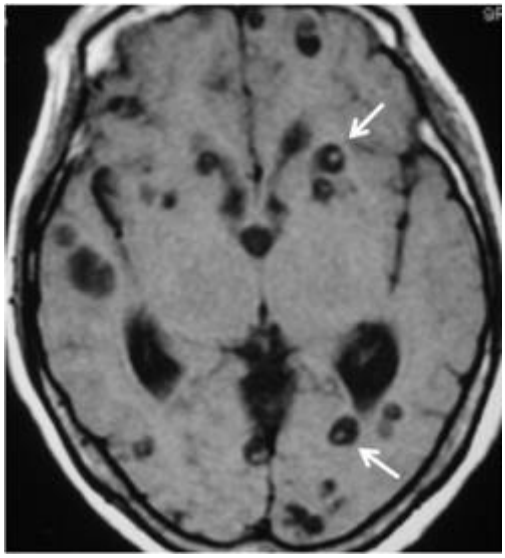

Fig. 5. Scolex producing the “hole-with-dot” imaging. Cited from “Del Brutto *et al.,* 2017”.

The majority of colloidal and granular cysticerci exhibit an enhanced ring-like or nodular shape following the intake of contrast media; these lesions are ill-defined and encircled by edema. According to Singh *et al.* (2010), this pattern's common name is "cysticercus granuloma." After the administration of contrast medium, calcified cysticerci show up on CT as tiny, hyperdense nodules that do not exhibit aberrant enhancement or perilesional edema (Del Brutto, 2022).

Hydrocephalus associated with inflammatory blockage of “Luschka and Magendie foramina” is the furthermost frequent feature in sub-arachnoid neurocysticercosis. According to Fleury *et al.* (2011), cystic lesions inside CSF cisterns function as mass-occupying lesions, segmental constriction, or blockage of intracranial arteries. They also typically have a multilobulated appearance and displace nearby structures.

Asymmetric hydrocephalus is caused by ventricular system distortion caused by ventricular cysticerci, which show up on CT as hypodense lesions. Due to differences in signal characteristics between the CSF and cystic fluid or scolex, most ventricular cysts can be seen on MRI. The "ventricular migration sign," which is the movement of the cysts inside the ventricular cavities in reaction to head movements, helps with diagnosis (Takayanagui and Haes, 2022).

4.2. Immunodiagnostic Examination:

Antibodies against *T. solium* species-specific antigens can be found, using the “enzyme-linked immuno-electro-transfer blot (EITB)” assay." Singh *et al.* (2010) have identified the primary drawback of this test, which is its potential for false negativity in as many as 50% of individuals suffering from a solitary cerebral cyst or calcifications on their own. However, patients who were exposed to the adult parasite but did not develop cysticercosis may test positive, which is another drawback. Nevertheless, antigen identification might be useful for tracking cysticidal medication effectiveness. The detection of circulating parasite antigens via the monoclonal antibodies screening method is insensitive for diagnosing neurocysticercosis (Garcia *et al.,* 2018; Arroyo *et al.,* 2022).

4.3. Stool Examination:

Neurocysticercosis patients have varying frequencies of positive *T. solium* egg results, which appear to be correlated with the infection's severity (Gilman et al., 2000).

4.4. ELISA and PCR:

When screening healthy people from endemic locations for *T. solium* carriers, specific antigen detection will be

more effective. Antigen testing can, however, be useful in diagnosing individuals with many cysts, most commonly those in the ventricular system or subarachnoid space, but it is only reliable in detecting infections that are still spreading. Viable parenchymal brain cysticerci can be distinguished from non-viable ones more effectively by combining data from ELISA antigen detection with neuroimaging (Toribio *et al.,* 2019).

According to a recent study, the diagnosis of NCC may additionally be achieved using a quantitative "polymerase chain reaction" (qPCR) technique. Subarachnoid as well as ventricular NCC can be diagnosed using this test, which is helpful (O'Connell *et al.,* 2020).

5. Management:

How well the cysts are able to survive depends on the quantity and distribution of lesions in addition to how successfully the host's immune system responds to parasites. Combining symptomatic and cysticidal medications is typically part of the therapy for neurocysticercosis patients, as not all of them respond well to a single therapeutic approach (Bustos *et al.,* 2016). As stated by Nash *et al.* (2006), surgery plays a part in the recovery of certain patients.

5.1. Symptomatic Treatment:

Due to neurological symptoms, patients who have symptoms of cysticercosis require medical care. As with medications for epileptic seizures, headaches, as well as other causes of intracranial hypertension, symptomatic treatment such as analgesics, steroids, mannitol, and antiepileptic medications is often recommended. Before thinking about starting antiparasitic medication therapy, it is crucial to properly establish symptomatic treatment (Coyle, 2019).

5.2. Cysticidal Drugs:

5.2.1. Praziquantel:

First-line treatment, administered every eight hours at a dose of "50 mg/kg" for a month. Praziquantel appears to work more effectively for those having just a single cyst in the brain parenchyma; patients with multiple cysts should use the 15-day trial. Results from Pretell et al. (2001) and De Brutto (2019) suggest that exposing cysticerci to three separate doses of "25 to 30 mg/kg" with two-hour intervals can sustain high medication concentrations for at least six hours, which may be enough to eradicate these parasites.

5.2.2. Albendazole:

The other cysticidal medication was first given at a dose of "15 mg/kg/day" for one month. If a patient just has one brain cyst, the course of treatment could be cut down to three days or even less than a week without compromising the medication's effectiveness. In studies evaluating the effectiveness of these medications, albendazole has been shown to be more efficient than praziquantel (Bustos *et al.,* 2005). The ability of albendazole to eradicate ventricular and subarachnoid cysts is an additional benefit. Higher dosages of up to "30 mg/kg" daily even prolonged, or repeated, treatments of albendazole might be required in some situations, especially in those with significant subarachnoid cysts (Fleury *et al.,* 2011).

Modern, carefully planned studies have demonstrated that the overwhelming majority of live cysticerci discovered in the parenchyma of the brain are eliminated by the usage of albendazole plus praziquantel drugs, which also relieves the clinical manifestations of patients (Garcia *et al.,* 2016).

5.2.3. Steroids:

When taking oral steroids, there was a decrease in the cumulative incidence of seizure recurrence over a period of 6–12 months and the incidence of clearance of non-calcified cysts has been increased. Following a 9-month follow-up period, another trial that used intravenous steroids found a decreased rate of seizure recurrence (Prakash *et al.,* 2006; Espino *et al.,* 2022). The commonly used parenteral steroids were intravenous dexamethasone "0.1 mg/kg" daily beginning one day before

antihelminthics medications; provide for 1 to 2 weeks, then taper. A daily dose of "1 to 2 mg/kg" of prednisolone (Zhao *et al.*, 2016).

Further studies are still required to evaluate the long-term antihelminthics efficacy, but overall, the combination use of steroids and antihelminthics appears to have a higher influence on preventing seizure recurrence.

5.3. Surgical Treatment:

In patients with NCC, surgery can be necessary. To treat hydrocephalus, the placement of a ventriculoperitoneal shunt is a more frequent technique than others. Additionally, during the last 20 years, neuroendoscopy emerged as the preferred method for managing intraventricular NCC. Though there is a chance of intraventricular bleeding when cysts are stuck to the ventricular wall, this method appears to be safe and effective. Therefore, vigilance is advised. Sometimes, big cysts or cyst masses are removed via open surgery; these are usually found in the fourth ventricle or the Sylvian fissures (Rajshekhar, 2010; Tan *et al.*, 2019).

6. Prevention and Control:

It is possible to eradicate neurocysticercosis. But eradication campaigns have to target all the interrelated stages of disease transmission, such as pigs carrying *Taenia* eggs in the environment, and carriers of the disease themselves. When the program is completed and there is inadequate covering of one of these disease transmission stages, there could be a rebound appearance of cysticercosis (Carabin *et al.*, 2018).

Public awareness campaigns, hygiene standards, proper meat handling, rigorous care of animals, and adherence to inspection protocols. In addition, Spreading Niclosamide or Praziquantel throughout the community to deworm them (Garcia *et al.*, 2021). This review addresses two more control-related factors. Firstly, vaccinations against illness in pigs. One such vaccine, TSOL18, uses an oncosphere antigen and has been proven to be quite efficient in preventing cysticercosis. The other is CystiHuman, the first model that simulates human NCC is created to assist in cost-benefit evaluations regarding cyst location, human NCC-associated manifestations, including the risk of seizures, management, as well as various NCC control measures (Bonnet *et al.*, 2022).

7. Concluding Remarks:

1. Data presented here evidently denotes that neurocysticercosis should be taken into consideration in the differential diagnosis of many neurological diseases because it frequently causes epileptic seizures along with various neurological signs.
2. Cercocycticidal therapy reduces the frequency of seizures and hastens the regression of lesions.
3. Reduced seizure recurrence appears to be achieved with antihelminthic/corticosteroid therapy.
4. A greater knowledge of the long-standing effects of cysticerci with calcification in the parenchyma of the brain is required because these conditions may be linked to subsequent hippocampal atrophy or sclerosis, recurrent migraines, or breakthrough seizures.
5. Future in-depth studies are crucial to explore and diagnose this neglected disease.
6. Prevention of NCC is important and feasible. In order to prevent and eradicate NCC, which would also help prevent epilepsy, efforts are required. Furthermore, populations that are economically engaged are the main groups affected by NCC-related epilepsy.

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