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Clinical symptoms, diagnosis, and treatment of neurocysticercosis

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Abstract

The infection of the nervous system by the cystic larvae of *Taenia solium* (neurocysticercosis) is a frequent cause of seizure disorders. Neurocysticercosis is endemic or presumed to be endemic in many low-income countries. The lifecycle of the worm and the clinical manifestations of neurocysticercosis are well established, and CT and MRI have substantially improved knowledge of the disease course. Improvements in immunodiagnosis have further advanced comprehension of the pathophysiology of this disease. This knowledge has led to individualised treatment approaches that account for the involvement of parenchymal or extraparenchymal spaces, the number and form of parasites, and the extent of degeneration and associated inflammation. Clinical investigations are focused on development of effective treatments and reduction of side-effects induced by treatment, such as seizures, hydrocephalus, infarcts, and neuroinjury.

Introduction

Neurocysticercosis is the infection of the CNS and its meninge coverings by the larval stage of the pork tapeworm *Taenia solium*. This tapeworm is endemic in most low-income countries where pigs are raised, and continues to be one of the most important causes of seizures in the world.[1] Industrialised countries are not free of neurocysticercosis, and it contributes, sometimes con siderably, to the burden of disease in patients with seizures or

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Declaration of interests

We declare no competing interests.

intracranial hypertension attending emergency rooms[2] or accessing neurological or neurosurgical services.[3] *T solium* infection is not endemic in the USA; therefore, neurocysticercosis cases are mainly due to immigration from endemic countries rather than local transmission. Despite this, the prevalence of neurocysticercosis is 0·2–0·6 per 100 000 inhabitants in some western states of the USA, and it is diagnosed in more than 2% of patients attending emergency rooms because of seizures.[4]

In the past few decades, the combination of modern diagnostic tests, use of antiparasitic drugs, improved anti-inflammatory treatments, and minimally invasive neurosurgery have improved the prognosis of patients infected with *T solium*. Despite these advances, neurocysticercosis is still the most common helminthic neurological infection and a major public health problem in most of the world. Millions of individuals are estimated to be infected, many of whom become symptomatic at some point in their lives.[5,6]. Without aggressive manage ment, which is not always available in many endemic areas, extraparenchymal neurocysticercosis is still associated with high mortality rates, mainly due to intracranial hypertension,[7,8] whereas mortality in parenchymal neurocysticercosis is limited to epilepsy-related deaths or a high burden of cysts.[9]

Neurocysticercosis is endemic in most Latin American countries, sub-Saharan Africa, and large regions of Asia, including the Indian subcontinent, most of southeast Asia, and China (figure 1). With increases in immigration from endemic regions, numbers of patients with neurocysticercosis are increasing in countries where local transmission is low.[5,11–13]

In most developing countries, neurocysticercosis is an important cause of admission to neurological hospitals and a major cause of adult-onset epilepsy. However, the number of symptomatic neurocysticercosis cases seems to be decreasing in some endemic regions, particularly in urban reference centres. Improvements to sanitation are likely to have had a major role in this reduction and the widespread use of antiparasitic treatment, given at early stages of disease in outlying, more rural clinics, could also be a contributor.[14,15]

Lifecycle of the parasite

T solium has a two-host lifecycle between human beings and pigs (figure 2). Human beings are the only definitive host for the adult tapeworm, whereas both pigs and human beings can be intermediate hosts that carry the larval form (cysticercus; figure 3). *T solium* larvae are cystic, fluid-filled membrane vesicles with a tapeworm head (scolex) inside. Normally, cysts are ingested in contaminated pork by a human host, after which the scolex evaginates, attaches to the intestinal wall by use of its effective suckers and hooks, and matures into a 2–4 m ribbon-like tapeworm. Gravid proglottids and micro scopic fertile eggs, each containing an infective embryo (oncosphere),[5] are passed to the environment in faeces. In places with poor sanitation and free-roaming animals, pigs have access to human faeces potentially containing *T solium* eggs. After ingestion, the embryos are released from the egg in the intestines and actively cross the intestinal mucosa to the bloodstream, which carries them to the peripheral tissues, including the CNS, where they develop into cysticerci.[17] Pigs that ingest infective eggs in human stools develop cysticercosis and become intermediate hosts. Therefore, infected pigs are a crucial component of the transmission cycle and ensure the

survival of *T solium*. The lifecycle is completed when people consume undercooked pork infected with cysts.

Similar to pigs, human beings can develop cysticercosis after ingestion of *T solium* eggs, which mostly occurs via the faecal-oral route from close contact with a tapeworm carrier. Exactly how and when transmission occurs is not known. Cysticercosis infections cluster around tapeworm carriers; person-to-person spread is more common than previously thought, particularly from people with many cysts, and is likely to be the predominate means of human contamination with *T solium* eggs rather than contamination through environmental sources.[18–20] Most investigators looking for the presence of *T solium* eggs in water or soil did not find them.[21,22] However, the role of environmental contamination as a means of infection has not been fully investigated and cannot be ruled out.

Natural history

In pigs, infective embryos entering tissues of the intermediate host encyst to form a cysticercus (figure 4).[23,24] However, only a few infective embryos form established cysts because most die during the process of establishment in the host;[25,26] whether infection is more effective in natural trans mission between human beings than in the animal host is unknown. Successful cyst development is likely to need active evasion of host immune mechanisms by the parasite, and many mechanisms of host manipulation by larval cysts to change the host response, enable survival, and control proliferation have been suggested. These include secretion of prostaglandins by the cysts[27] and inhibition of effective immune responses, including depression of the host's proliferative responses.[28–34] Additionally, the blood–brain barrier restricts access of the immune response to the brain and might protect the parasite from attack by the host's immune system. Cysts can remain viable for years, but they eventually begin to degenerate, invoking a strong host inflammatory response and granuloma formation. The vesicular cyst first passes into the colloidal stage, where it is surrounded by a well defined inflammatory capsule, formed by a cellular inflammatory reaction (composed of plasma cells, lymphocytes, macrophages, and eosinophils). This reaction also involves the internal structures of the parasitic cyst, resulting in the cyst fluid becoming dense and turbid. In this late colloidal stage the larvae are no longer viable. Changes around the degenerating cyst include proliferation and activation of astrocytes and microglia, neuronal degeneration and oedema, and perivascular lymphocytic infiltrates of nearby blood vessels. Thereafter, the cyst collapses and its membranes and scolex are replaced by fibrotic tissue. Inflammation and oedema gradually subside. Astrocytosis persists and even increases, and multinucleated giant cells are formed. Degenerating cysts eventually develop into calcified nodules, and although many calcified cysticerci have little associated inflammation, some might have residual inflammation associated with blood–brain barrier disruption.[35] The stage of degeneration and degree of inflammation can be assessed by MRI, which can be used to monitor the effectiveness of treatment.

Clinical manifestations

Overview

Hallmarks of neurocysticercosis include variation in manifestations and disease severity. Clinical manifestations can vary from completely asymptomatic infection to severe disease and death. Disease severity and clinical manifestations are indicative of the characteristics of infection (number, size, and location of cysts and intensity of the host's immune response). In endemic areas, neurocysticercosis is regarded as the great imitator because it can mimic almost any neurological disorder.[36] The major determinant of the characteristics of symptomatic neurocysticercosis is whether the parasites are located in the brain parenchyma or in the extraparenchymal spaces.[37] Generally, parenchymal brain cysticercosis presents with seizures as the major manifestation, but seizures usually respond well to antiepiletic drugs. However, viable cysts might survive for years or even decades with intermittent neurological symptoms. Conversely, extra parenchymal neurocysticercosis has a worse prognosis, with very high mortality rates of around 20% in those who do not receive optimum treatment, which is not available in most endemic areas.[7,38,39]

Although no pathognomonic clinical picture exists, in endemic regions adult-onset seizures are highly suggestive of neurocysticercosis. A review by Carabin and colleagues[40] showed that recurrent seizures occur in about 80% of symptomatic cases of neurocysticercosis, which is in agreement with previous findings that epilepsy is the most common manifestation of neurocysticercosis. Other manifestations include focal neurological deficits (16%), increased intracranial pressure (12%), and cognitive decline (5%).[40] Cysticercosis outside the CNS is not usually associated with clinical manifestations, with the exceptions of ocular cysticercosis and rare cases with massive muscular involvement.

Cysticercosis can affect men and women from infancy to old age, with a peak incidence at ages 20–50 years. However, clinical manifestations of the disease are different in infants and children than adults.[41] Single, enhancing nodules are more frequent in people younger than 30 years, subarachnoid neurocysticercosis mostly presents in older age groups, and neurocysticercosis-associated inflammation tends to be more severe in children and women.[42–46] The reasons for these findings are not fully understood. However, the interaction of several factors, including variations in native versus acquired immune responses and age-related or sex-related differences in reactivity of the immune system, could be responsible for age and sex-related differences in the pattern of disease expression.

The prognosis of neurocysticercosis varies in accordance with the location and burden of parasites. Sub arachnoid and intraventricular neurocysticercosis are associated with substantial mortality and serious morbidity.[7,8] The prognosis in parenchymal brain cysticercosis is mostly affected by the number of lesions and extent of inflammation. Individuals with one brain lesion have a very good chance of survival with no seizure relapses,[47] whereas many cysts in the brain can be lethal or result in recurring seizures. Although data from controlled trials are not available, published case series suggest that the prognosis of neurocysticercosis has improved, probably because of better diagnostics and improved disease management.[12,14,15]

Seizures or epilepsy

Epilepsy is defined as two or more unprovoked seizures that occur more than 24 h apart.[48] Recurrent seizures are most often the main or sole manifestation of parenchymal brain cysticercosis. In most endemic countries, neurocysticercosis occurs in about 30% of patients with epilepsy or patients who present with seizures.[6,49–51] Although results of some studies have shown that most patients with neurocysticercosis-related epilepsy have generalised seizures, most patients are likely to have had partial seizures with rapid secondary generalisation. Seizures are a very frequent manifestation in patients with degenerating cysts. Mechanisms of epileptogenesis in neurocysticercosis are the subject of debate, and are likely to include local inflammation and the formation of reactive gliotic scars.[52] Seizures might initially occur when parasites begin to degenerate; however, case series have shown that seizures might un commonly occur in patients who have only vesicular cysts, without contrast enhancement or perilesional oedema, at the time of diagnosis.[53] Mild inflammation around these cysts that is not detected by MRI cannot be ruled out.[54]

Patients with calcified parenchymal brain cysticerci present with recurrent seizures;[55] around 35–50% of cases are associated with contrast enhancement and evident perilesional oedema.[33,56,57] The pathophysiology of perilesional oedema is unclear, but is probably inflammatory. This inflammation is due to inter mittent host responses to antigens trapped in the calcium matrix or from the loss of inhibition or suppression of the host's immune response.[58] Seizure recurrence rates are best defined for single enhancing lesions, but can vary substantially,[59] perhaps because of the different treatments. Rates of seizure relapses at 6–12 months after initiation of treatment vary and range from 13% to 48% in patients with a single granuloma,[60–63] from less than 10% to 34% in patients with only calcified lesions, [35,60] and 54% in patients with multicystic disease.[53] Development of residual calcification after resolution of a viable or degenerating cyst is a risk factor for further seizure episodes.

Up to 40% of patients (18 of 45) in the study with cysticercosis-related medically intractable epilepsy had calcifications associated with ipsilateral hippocampal sclerosis,[64] suggesting that neurocysticercosis might be causal or contribute as a dual pathology for antiepileptic drug (AED)-resistant epilepsy in these cases.[65,66] In this study, calcified neurocysticercosis was the cause of drug resistant epilepsy in 17 patients, was associated with unilateral hippocampal sclerosis in another 18 patients, and was regarded as an incidental finding in ten patients. Overall, about 1% of patients with drug-resistant epilepsy assessed for surgery had calcified neurocysticercosis.[64] Calcified neurocysticercosis accounts for a large proportion of clinical cases at presentation, and many patients with degenerating cysts will develop calcified lesions. Understanding of the mechanisms associated with seizures in calcified neurocysticercosis and the provision of appropriate anti-inflammatory, immunological modulating, and antiseizure therapies might substantially reduce the overall burden of disease.

Focal neurological deficits

Neurocysticercosis can cause almost any focal deficit of central origin. Focal neurological deficits could be due to the presence of parenchymal brain cysts or, most often, to deleterious effects of pericystic oedema or mass effects of large subarachnoid cysticerci.

Patients with neurocysticercosis and arachnoiditis might present with focal signs and ischaemic strokes related to the occlusion of small and medium intracranial arteries, entrapment of cranial nerves resulting in paralysis of extraocular muscles, hearing loss, facial nerve palsy or trigeminal neuralgia, and focal neurological symptoms related to brainstem compromise. Radicular pain, weakness, and sensory deficits are common in patients with cysticercosis of the spinal cord, and are mostly related to local mass effect or inflammatory changes in the spinal subarachnoid space.[5,67,68]

Intracranial hypertension

Increased intracranial pressure in patients with neurocysticercosis can result from various pathogenic mechanisms. The most common mechanism is hydrocephalus, which can be due to cysts or inflammation causing mechanical blockage of any of the ventricles or the aqueduct of Sylvius, occlusion of the foramina of Luschka, the foramina of Magendie, or the foramina of Monroe, or by communicating hydrocephalus (which is frequent in neurocysticercosis arachnoiditis).[69] The clinical course of intracranial hypertension and hydro cephalus secondary to basal arachnoiditis might be subacute or chronic, whereas hydrocephalus related to fourth ventricle cysts might present with Bruns' syndrome (sudden loss of consciousness related to head movements). Hydrocephalus in neurocysticercosis is associated with high mortality rates, except when neurosurgery is available.[70,71] Additionally, cerebral aqueduct stenosis can be associated with paroxysmal headaches and Parinaud's syndrome. Mass effect with intracranial hypertension can also develop secondary to large subarachnoid cysts or cyst clumps, which frequently develop in the Sylvian fissure or in the basal cisterns of the brain, with or without resulting hydrocephalus.[8] Finally, intracranial hypertension might be due to so-called cysticercotic encephalitis, a severe form of parenchymal neurocysticercosis that usually affects children and young women in the first three decades of life. Patients with cysticercotic encephalitis have hundreds of small, viable, or degenerating cysts with a diffuse inflammatory reaction. These patients present with cloudiness of consciousness with acute or subacute onset that is associated with seizures and intracranial hypertension.[46] Widespread infections suggest a high level of exposure, which occurs in patients with taeniasis.[72,73]

Cognitive decline

Various degrees of impairment in cognitive function might occur in patients with neurocysticercosis, from subclinical deficits to marked dementia.[74–76] Before the introduction of modern neuroimaging studies, some patients with neurocysticercosis were committed to psychiatric hospitals. In these cases, the correct diagnosis was suspected only after patients had developed seizures or intracranial hypertension. So-called psychotic episodes in parenchymal neurocysticercosis could represent attacks of psychomotor epilepsy or postictal psychosis. Poor hygiene could increase the risk of neurocysticercosis infection in patients with psychosis.

Other manifestations

Although neurocysticercosis might present as almost any neurological symptom, patients with headache as an isolated symptom,[77,78] associated stroke,[79] or involuntary movements[80] are frequently seen.

Diagnosis

Challenges

Histological confirmation of the parasite is not possible in most cases; therefore, diagnosis is usually based on neuroimaging and confirmed by serology. Despite modern neuroimaging methods and reliable immune diagnostic tests, diagnosis of neurocysticercosis can still be a challenge because of the poor specificity of clinical and neuroimaging findings and suboptimum predictive values in immunodiagnostic tests, particularly in endemic settings.

Neuroimaging diagnostic investigations

CT and MRI show the morphology and localisation of cysts, burden of infection, stage of the cysts, and the presence of surrounding inflammation (figure 5). How the parenchymal brain lesions look on neuroimaging indicates their stage of involution, although precise staging is not always clear because parasite degeneration is a continuum rather than a staged process. Live vesicular cysts are small and rounded lesions with little or no pericystic oedema and are not enhanced with contrast. The cysts frequently show the tapeworm scolex as an internal asymmetric nodule in the cyst (hole-with-dot), and several viable cysts showing scolices confirm the diagnosis. After the degenerative process becomes established (colloid cysts), the cysts have poorly defined borders, are surrounded by oedema, and show marked ring or nodular contrast enhancement. One degenerating cyst might pose a diagnostic problem and even lead to unnecessary biopsies.[81] Diffusion-weighted images and apparent diffusion coefficient maps might allow visualisation of the scolex in colloidal cysticerci, which is rarely visible on CT or conventional MRI sequences. Nodular lesions (without discernible fluid contents) are most likely to correspond with the granular stage and could be surrounded by hyperintense rims representative of gliosis. Calcified cysticerci are clearly visible on CT as non-enhancing hyperdense nodules, usually without peripheral oedema. Although conventional MRI sequences are not as sensitive as CT to detect calcified cysticerci, the sequences might improve with the use of susceptibility-weighted image protocols.[82,83]

Small, cystic, subarachnoid cysticerci located within cortical sulci generally behave as parenchymal brain cysts: they remain cystic, do not grow, and eventually degenerate and disappear or become a residual calcified scar. Cysticerci can present with similar findings to those described for parenchymal cysts—ie, viable, degenerating, or calcified lesions. Conversely, cystic lesions within the Sylvian fissures or the basal CSF cisterns might displace neighbouring structures because they reach a large size, and can have a multilobar appearance (the so-called racemose form of neurocysticercosis). Subarachnoid neurocysticercosis is frequently associated with hydrocephalus caused by inflammatory occlusion of ventricular foramina, more widespread arachnoiditis, or mass effects. Arachnoiditis is visible on CT or MRI studies as areas of abnormal leptomeningeal enhancement at the base of the brain.[82–85] Basal subarachnoid neurocysticercosis is associated with spinal involvement in about 60% of cases.[68]

Intraventricular and cisternal cysts are clearer on MRI by use of FLAIR (fluid attenuated inversion recovery), FIESTA (fast imaging employing steady state acquisition sequence),

CISS (constructive interference in steady state), or BFFE (balanced fast field echo) protocols.[83,86,87] They are infrequently visualised on CT because they are isodense with the CSF, and therefore usually manifest on CT solely as enlarged ventricles or hydrocephalus,[87–89] although distortion of the sub arachnoid space without discrete cysts might be seen. MRI is best for imaging cysticercosis of the spinal cord or the spinal subarachnoid space because it provides greater definition of lesions. Lepto meningeal cysts are seen on MRI as cystic lesions or areas of arachnoiditis, and intramedullary cysticerci are seen as rounded cysts with an internal scolex. Cysts without an identifiable scolex could be mistaken for spinal tumours.[68]

Immunological diagnosis

The best documented serological test is the enzyme-linked immunoelectrotransfer blot (EITB) assay, which uses lentil lectin purified glycoprotein antigens (LLGP) to detect antibodies to *T solium* in serum. EITB sensitivity is around 98% for patients with two or more live parasites in the nervous system, thus people with more than one viable cyst or subarachnoid disease at the time of testing will have a positive serology. EITB does not cross-react with heterologous infections.[90] A negative serology in patients should lead to the investigation of alternative diagnoses. The sensitivity of antibody detection by EITB seems to be slightly lower in CSF than in serum (90% *vs* 100%).[91] A major weakness of EITB is its low sensitivity (50–60%) in patients with one intracranial cysticercus; therefore, a negative test cannot exclude neurocysticercosis. The sensitivity of antibody detection assays, including the EITB, is poor in patients with calcified cysticerci.[91,92] However, antibodies to *T solium* are frequently reported in the asymptomatic general population in endemic regions; their presence can suggest exposure to the parasite or current or past asymptomatic infections. Since antibody assays show cysticercus infection, the sera of any patient with muscular or subcutaneous cysticercosis, but no brain involvement, might test positive, thereby lowering the specificity of these assays to diagnose neurocysticercosis.

Detection of anticysticercal antibodies in the CSF by ELISA is 89% sensitive and 93% specific in patients with viable neurocysticercosis infections, and is still used when EITB is not available.[93] ELISA is more reliable in CSF than in serum because of improved specificity, and its sensitivity in CSF to detect subarachnoid neurocysticercosis is similar to that of the EITB.[94] ELISA results, similar to those from an EITB test, are frequently negative in patients with only a few parenchymal cysts and in those with only calcified disease, and there might be cross-reactivity in sera from patients with helminthic infections.[92]

Detection of circulating parasitic antigens in serum by ELISA with monoclonal antibodies has been used in clinical and field studies. Circulating antigens are present only in the serum of patients with viable parasitic tissue, and serum concentrations rapidly decrease after successful antiparasitic treatment or surgery.[95,96] Initial reports used this assay in CSF specimens,[97] but the duration of antigens in CSF is not known.[92,98] The sensitivity of this test in serum for parenchymal neurocysticercosis is poor—ranges from 72% to 86%—and is commonly negative in patients with one or a few live cysts. ELISA could be useful to monitor the decrease in parasite burden in response to antiparasitic treatment in people with

extensive disease and, in particular, those with subarachnoid neurocysticercosis.[92,95,96] Circulating anti gens are almost always present in patients with basal subarachnoid neurocysticercosis and in most patients with racemose involvement of the subarachnoid spaces. In our experience, quantitative serial serum ELISA assays are helpful to determine a response to treatment in sub arachnoid neurocysticercosis.

Other diagnostic tests

Peripheral eosinophilia can be reported in neurocysticercosis, although this is uncommon and when present there are not markedly high concentrations of eosinophils (around less than or equal to 10%). Nonspecific CSF abnormalities are common in neurocysticercosis, although they are more frequent in patients with active inflammation or multiple lesions, or in those with ventricular or subarachnoid disease. Common CSF abnormalities include mononuclear pleocytosis (usually lower than 300 cells per mL) and a mild increase in CSF protein concentrations (commonly between 50 mg/dL and 300 mg/dL). Low CSF concentrations of glucose have been associated with a poor prognosis.[99] PCR assays for *T solium* DNA have been assessed, mainly in CSF, with variable results.[92]

Concurrent intestinal taeniasis in patients with neurocysticercosis is uncommon, indicating that the lifespan of cysticercus and the prepatent period are likely to be longer than that of the adult tapeworm. Most series report concurrent intestinal taeniasis in 5% or less of cases, although a systematic search might increase this proportion up to 10%. The frequency of intestinal taeniasis seems to be related to the severity of neurocysticercosis infection; the greater the infestation in the brain, the greater the chance that the patient also has taeniasis through self-infection.[72,73] Young patients and those with many cysts are more likely to carry a tapeworm than are patients with calcified disease. Taeniasis should be assessed in household members and contacts of paediatric patients because the infective tapeworm is likely to be alive within the short time between infection and clinical presentation. Recognition of *T solium* eggs by coproparasitological studies has poor sensitivity. Specific coproantigen detection by ELISA has improved screening for *T solium* carriers and also can confirm the efficacy of treatment in intestinal taeniasis.[100,101]

Both neurocysticercosis and tuberculosis are commonly encountered in low-income regions of the world and have some similar clinical and radiological features. Diagnostic criteria have been validated to differentiate these entities in patients with one brain nodule on the basis of size, oedema, and clinical presentation.[102] In 2001, diagnostic criteria for neurocysticercosis were published that used objective clinical, radiological, immunological, and epidemiological data.[103] These criteria are categorised on the basis of their diagnostic strength as absolute, major, minor, or epidemiological, and their interpretation allows assignment to either definitive or probable neurocysticercosis (panel). These diagnostic criteria were promptly adopted by the medical community[104–107] as a practical standard for the diagnosis of neurocysticercosis. Although not systematically validated, because of the absence of a comparative gold standard, these criteria have become highly useful in the diagnosis of neurocysticercosis. However, some authors have raised concerns about their validity and applicability.[108] Newly developed immuno-diagnostic tests and imaging techniques might help to improve the criteria in the near future.

Treatment

Parenchymal neurocysticercosis

Before therapy is planned, proper characterisation of the specific type and brain involvement of neurocysticercosis is important.[42] Therapeutic approaches might include symptomatic therapy, antiparasitic treatment, or surgery (lesion resection or shunt placement), and often more than one of these options are needed (table).

Generally, patients with neurocysticercosis and epilepsy respond well to first-line AEDs and, with the exception of patients with one degenerating parasite that resolves without calcification, they should receive AED therapy for at least 2 years after the last seizure, followed by gradual withdrawal, such as in other seizure disorders.[109,110] Seizures in patients with pure viable or calcified forms of neurocysticercosis have been suggested to represent true epilepsy, whereas seizures in patients with degenerating cysts should be interpreted as symptomatic seizures, and therefore patients should receive AED therapy for much shorter periods.[111,112] This claim is based on the positive prognosis of patients with one enhancing cysticercus, whereas most seizure relapses are associated with the presence of residual calcification;[113] therefore, AEDs can be safely withdrawn in more than 85% of cases once the granuloma has resolved on imaging.[47] However, withdrawal is not recommended in patients with multicystic disease because most of these patients will end up with calcified lesions, and a substantial proportion will have further seizure relapses. Similarly, studies in patients with symptomatic calcified neurocysticercosis show a high risk of seizure relapses after AED withdrawal, which is routinely indicated in patients who did not have any seizures for 2 or more years.[114] In the wait for the results from large controlled studies, present recommendations for AED therapy in neurocysticercosis should not differ from those in other secondary epilepsies.

In highly endemic areas, parenchymal brain calcifications can be a common incidental finding on neuroimaging.[49–51] Although the actual risk of epilepsy in asymptomatic individuals with such brain calcifications is unknown, prophylactic AED therapy is not justified. Asymptomatic individuals with viable cysts are quite rare. However, viable cysts can be present in otherwise healthy individuals who undergo neuroimaging studies because of head trauma or other unrelated conditions.[78] Although no controlled data exist for antiparasitic treatment of asymptomatic viable neurocysticercosis, seizure onset after antiparasitic treatment has been reported in several cases.[115,116] Therefore, if antiparasitic treatment is deemed appropriate, AED treatment for at least a few months could be regarded as reasonable.

Perilesional brain inflammation is present (to some extent) in almost all cases of neurocysticercosis.[117] In intraparenchymal neurocysticercosis, perilesional inflammation can be present at any stage of the cyst lifecycle, although it is unusual in viable cysts before the onset of symptoms.

Substantial oedema can occur around calcified lesions, and steroids can help in the acute management of symptoms secondary to moderate or severe perilesional oedema developing around one or more cysts. However, the benefit of steroids in this instance is unclear, and

symptomatic rebound oedema might occur with abrupt cessation of steroids without a taper.[118] Long-term benefits of anti-inflammatory therapy (in the absence of antiparasitic treatment) have only been assessed in the management of single degenerating cysts, with conflicting results.[59,113]

Symptom exacerbation is common during the first week after antiparasitic treatment is initiated. The use of steroids decreases side effects. Many variations of steroidal drugs, doses, and lengths of treatment have been used. The most common regimen is 0·1 mg/kg per day of dexamethasone given 1 day before antiparasitic therapy commences and maintained for 1 or 2 weeks, followed by a slow taper.[117] Seizures and other neurological symptoms might relapse by the time of dose reduction, so a slow taper might reduce these sypmtoms. Increases in the dose of concomitant steroids result in fewer seizures for the first 21 days during and early after antiparasitic treatment.[119]

Antiparasitic drugs destroy the parasites (figure 6), but can also lead to temporary inflammation and increased severity of symptoms of neurocysticercosis. Thus, there is no particular advantage to initiation of antiparasitic treatment immediately after diagnosis, before the symptoms are under control. Whether the destruction of brain cysts improves the prognosis of the secondary seizure disorder has been questioned by some authors.[120] Vesicular cysts have reached a state of immune tolerance with the host. Follow-up of untreated patients in one placebo-controlled trial[53] did not show significant degeneration of viable cysts during 6 months, so spontaneous resolution is not expected in the short term. The use of antiparasitic drugs in such cases is supported by level 1 evidence (one or more well designed radomised clinical trials or a well completed meta-analysis), because this approach provides clinical improvement and resolution of lesions in most patients compared with placebo or no therapy.[53] Antiparasitic treatment is partly effective, destroying 60–80% of cysts and achieving the resolution of all viable intraparenchymal cysts in less than 40% of cases, with a slightly higher efficacy for albendazole (usual dose 15 mg/kg per day for 2 weeks) than praziquantel (usual dose 50 mg/kg per day for 2 weeks).[53,121–123] In patients with one cyst, regimens of albendazole for 3 days or a 1-day course of praziquantel therapy could be as effective as longer regimens.[124,125] Doses of praziquantel for neurocysticercosis have not been systematically standardised. Colloidal cysts are degenerating parasites and the natural history of most of these lesions is further degeneration and calcification.[113] However, level 1 evidence also supports the use of antiparasitic drugs in patients with colloidal cysts, because several double-blind trials showed that the use of albendazole not only results in enhanced resolution of colloidal cysticerci, but also in a reduction of the risk of seizure recurrence in most patients.[59,126] Combinations of two antiparasitic drugs could damage the parasite by different mechanisms and increase cysticidal efficacy. Albendazole given with praziquantel is safe, and the simultaneous administration of praziquantel increases albendazole serum con centrations by 50%.[36] In a study by our group, combined albendazole with praziquantel greatly increased cyst resolution in patients with three or more cysts, and showed that resolution of all viable cysts is associated with fewer partial seizures during an 18-month period after treatment (unpublished data, CWGP [cysticercosis working group in Peru] 2013). Despite total parasite resolution, a proportion of patients will still have seizure relapses, most likely due to recurring inflammation around remnant scars or residual perilesional gliosis. There are no controlled trials testing the efficacy of either drug in cysts

previously unaffected by an initial antiparasitic course. Early imaging or immune markers of efficacy of antiparasitic treatment could help to shorten the time to cyst disappearance by prompting early retreatment.

Calcifications represent sequelae of previous infections, and patients with only calcified lesions should not receive antiparasitic treatment. Antiparasitic drugs should not be used in patients with cysticercotic encephalitis because they might potentiate the already excessive inflammatory response within the brain parenchyma that occurs in this severe form of neurocysticercosis. In patients with cysticercotic encephalitis, corticosteroids, osmotic diuretics, and decompressive craniotomy are advised to control brain oedema and to avoid the life-threatening risk of intracranial hypertension.[99]

Extraparenchymal neurocysticercosis

Extraparenchymal neurocysticercosis lesions can localise to the subarachnoid space of the convexity of the cerebral hemispheres, in the Sylvian fissures, in the basal cisterns, or in the ventricular cavities.[8] Medical treatment of small subarachnoid cysts localised to the convexity of the cerebral hemispheres is similar to that described for parenchymal brain cysts.[127] Treatment of giant cysts in the Sylvian fissure is controversial (level 3 evidence [provided by expert opinion or open-case series]). Although some authors recommend surgical resection of these lesions, others suggest medical therapy with albendazole and corticosteroids might be an equally effective but less aggressive approach.[128] High doses of albendazole, prolonged courses of therapy, or repeated cycles are usually needed in patients with basal subarachnoid cysticercosis. Inflammatory reactions that occur because of cyst degradation might result in endarteritis, thrombosis, ischaemia, or (less frequently) haemorrhagic stroke. Routine corticosteroid administration is mandatory in patients with subarachnoid cysts, to avoid the risk of cerebral infarction.[129] Side-effects of long-term steroids can be severe and incapacitating. Methotrexate seems useful as a replacement for steroids or as a steroid-sparing agent in patients with subarachnoid cysts, although more extensive experience with this drug is needed.[130] Because of the aggressive nature of extraparenchymal neurocysticercosis, no evidence is based on controlled clinical trials. With exception of a subgroup analysis in a trial,[122] which showed non-significantly increased rates of disappearance of extraparenchymal cysts in patients given antiparasitic treatment (46% treatment *vs* 27% control groups at 6 months [p=0·164], which decreased to 58% *vs* 50% at 12 months [p=0·578]), all existing evidence is from case series.

Intracranial hypertension can be caused by cysticercotic arachnoiditis, mass effect of cysts located in basal subarachnoideal cisterns, or the obstruction of CSF pathway by ventricular cysts. Similar to other causes of intracranial hypertension, resolution of intracerebral haemorrhage is crucial and urgent in patients with hydrocephalus secondary to neurocysticercosis. Immediate CSF drainage or shunt placement is needed for most cases of hydrocephalus because of subarachnoid neurocysticercosis, although high dose corticosteroids (dexamethasone, 16 mg/kg per day or more) frequently lead to temporary control of hydrocephalus. Neuroendoscopy with third ventricle fenestration might stop the need for a shunt device, probably improving the patient's prognosis, because shunt malfunction or infection is a common cause of morbidity. Mortality has been related to the

number of shunt revisions patients have undergone,[131] but oral prednisone might reduce the risk of shunt dysfunction (level 3 evidence)[132] Chronic steroid treatment could be a risk in regions with high rates of latent tuberculosis and strongyloidiasis. Non-controlled reports in the USA suggest that shunt failures are less common with aggressive management, including intensive antiparasitic and anti-inflammatory therapy (often with methotrexate as a steroid-sparing agent), together with shunting.

Ventricular cysticercosis could be treated by surgical resection or by antiparasitic treatment. Although some reports suggest that albendazole therapy destroys ventricular cysts, consensus guidelines (based on level 3 evidence) favour surgical resection of most of these lesions, with the possible exception of small cysts located in the lateral ventricle.[127] The favoured surgical approach is endoscopic removal of cysts in the lateral and third ventricles with a flexible ventriculoscope, and a posterior approach for removal of fourth ventricular cysts. Endoscopic exploration of the ventricular cavities is less invasive, obviates long-term use of albendazole and corticosteroids, frequently identifies small additional cysts not seen on neuroimaging, prevents the possibility of cyst migration within the ventricular cavities from diagnosis to surgery, and can be complemented by fenestration of the base or anterior wall of the third ventricle, preventing the need for a shunting device.[70,133–135] Fourth ventricle cysts can be removed by neuroendoscopy, either from above through the aqueduct, via a suboccipital approach, or alternatively by open microsurgical dissection. Caution should be taken with cysts adhered to the ventricular wall because of the possibility of bleeding. In patients without associated ependymitis, permanent shunting procedures in addition to endoscopical removal might not be necessary.

Cysticercosis in other CNS locations

The present accepted therapy for intramedullary cysts and cysts in the spinal subarachnoid space is surgical resection of the lesion (level 3 evidence). A systematic review[136] showed albendazole is an option for therapy of intramedullary spinal cord cysts; however, these data might be affected by publication bias. Further experience with medical treatment is needed before a clear recommendation can be made for surgical or medical approaches to treat this form of the disease. Spinal subarachnoid cysts might migrate, hence neuroimaging studies should be done immediately before surgery. Prognosis after surgery is usually good unless prolonged compression of spinal nerve roots occurred before diagnosis. Although surgical management is the standard of care for ocular cysticercosis, occasional reports show success with steroids and antiparasitic drugs.[137]

Parasite control and potential elimination

T solium infection is one of a few diseases targeted for focal elimination and eventual eradication by the International Task Force for Disease Eradication.[138] Several factors make this removal feasible: human beings are the only definitive host; the intermediate host is a domestic animal whose exposure to ova can be controlled; sensitive diagnostic tests for taeniasis and cysticercosis allow identification of infected people and pigs; good treatment regimens are available for taeniasis and porcine cysticercosis; and pig vaccines were highly efficacious under controlled and field conditions.[139,140] Field control efforts have been

attempted since 1987 in several Latin American countries, including Ecuador, Mexico, Peru, Guatemala, and Honduras, and recently in some African settings.[141,142] Our group in Peru undertook a very large scale elimination programme encompassing an entire region with 70 000 rural inhabitants. Preliminary results showed that interruption of transmission is feasible (unpublished data, CWGP 2013). Efforts for expansion of elimination need to consider local particularities of pig raising and trade, migration pathways, and cultural aspects affecting the compliance with elimination methods.

Conclusions and future directions

Neurocysticercosis affects many people in most developing countries and is reported with some frequency in industrialised countries. Substantial progress has been made to understand the characteristics of infection and disease, particularly in relation to improved definition of disease subtypes and individualised diagnostic and management approaches, such as increased attention to the role of anti-inflammatory therapy, new evidence of the benefits of resolving intraparenchymal cysts in terms of future seizures, and recognition of calcified neurocysticercosis as a continuous source of seizures in many cases. This progress has led to a greatly improved prognosis for most patients. Simultaneously, pilot control strategies have been successfully tested in diverse settings. Further research is needed to provide evidence-based diagnostic techniques and therapies; aetiological diagnostic confirmation of patients with one brain lesion continues to be elusive, antiparasitic treatment still yields suboptimum results, and minimum to no controlled information in many other aspects exists, including about how to modulate the inflammatory response to the dying parasite. Neurocysticercosis can also be con ceptualised as a human model for development of seizures and epilepsy, and properly designed studies should yield valuable information about genetic predisposition, pathological mechanisms, and potential therapeutic targets for chronic epilepsy. Finally, if local elimination of transmission is confirmed and replicated, this will open the door to cysticercosis eradication efforts worldwide.

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Panel: Diagnostic criteria for neurocysticercosis

Absolute

- Histological proof (biopsy of a brain or spinal cord lesion)
- Cystic lesions with scolex on neuroimaging
- Retinal cysticercosis visible on fundoscopic examination

Major

- Lesions highly suggestive of neurocysticercosis on neuroimaging
- Positive serum antibodies on enzyme-linked immunoelectrotransfer blot
- Cyst resolution after antiparasitic treatment
- Single brain enhancing lesion spontaneously resolved

Minor

- Suggestive lesions on neuroimaging
- Suggestive clinical manifestations
- Positive CSF antigen or antibodies on ELISA
- Extraneural cysticercosis

Epidemiological

- From or living in an endemic region
- Frequently travels to disease-endemic areas
- Household contact with taeniasis

Adapted from Del Brutto.[103]

Search strategy and selection criteria

We searched for articles published before Nov 1, 2013, in English, Spanish, Portuguese, or Italian. We selected articles from Medline by use of the PubMed system with search terms "cysticercosis", "neurocysticercosis", "*Taenia solium*", "epilepsy", or "seizures". Additional references were obtained from the personal archives of authors or manual searches of references from identified articles during 2014.

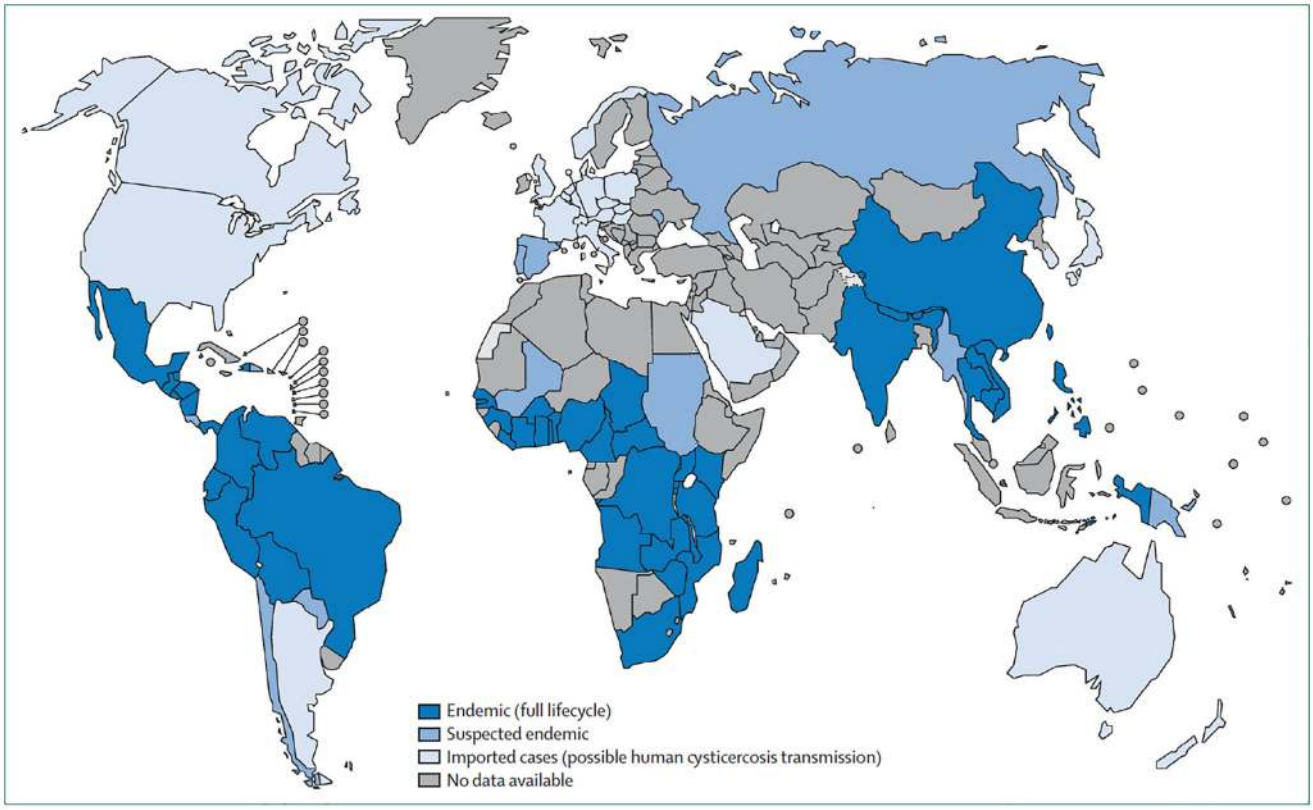

Figure 1: Geographical prevalence of *Taenia solium*

Reproduced from the *First WHO report on neglected tropical diseases*[10] by permission of the World Health Organization.

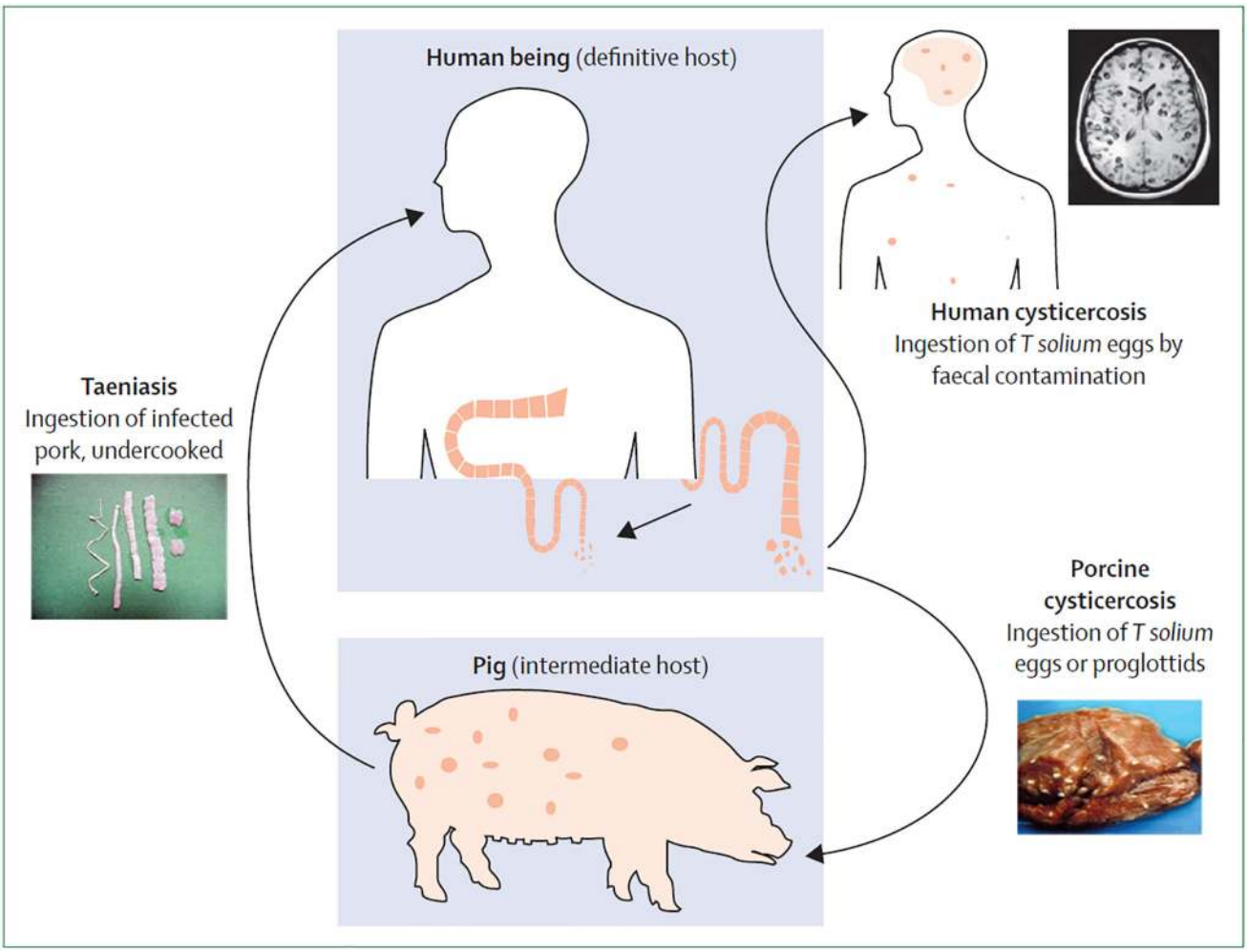

Figure 2: Lifecycle of *Taenia solium*
Reproduced and adapted from Garcia and colleagues.[16]

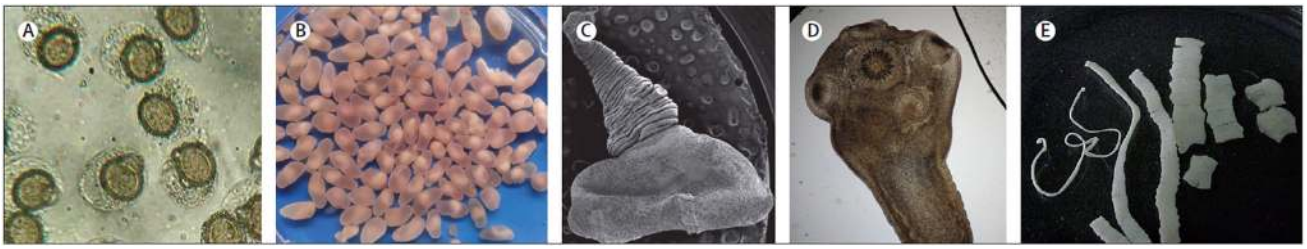

Figure 3: Growth stages of *Taenia solium*

Infective *T solium* egg (A), larva or cysticercus (B), evaginating cysticercus (C), tapeworm scolex (D), and tapeworm strobila (E).

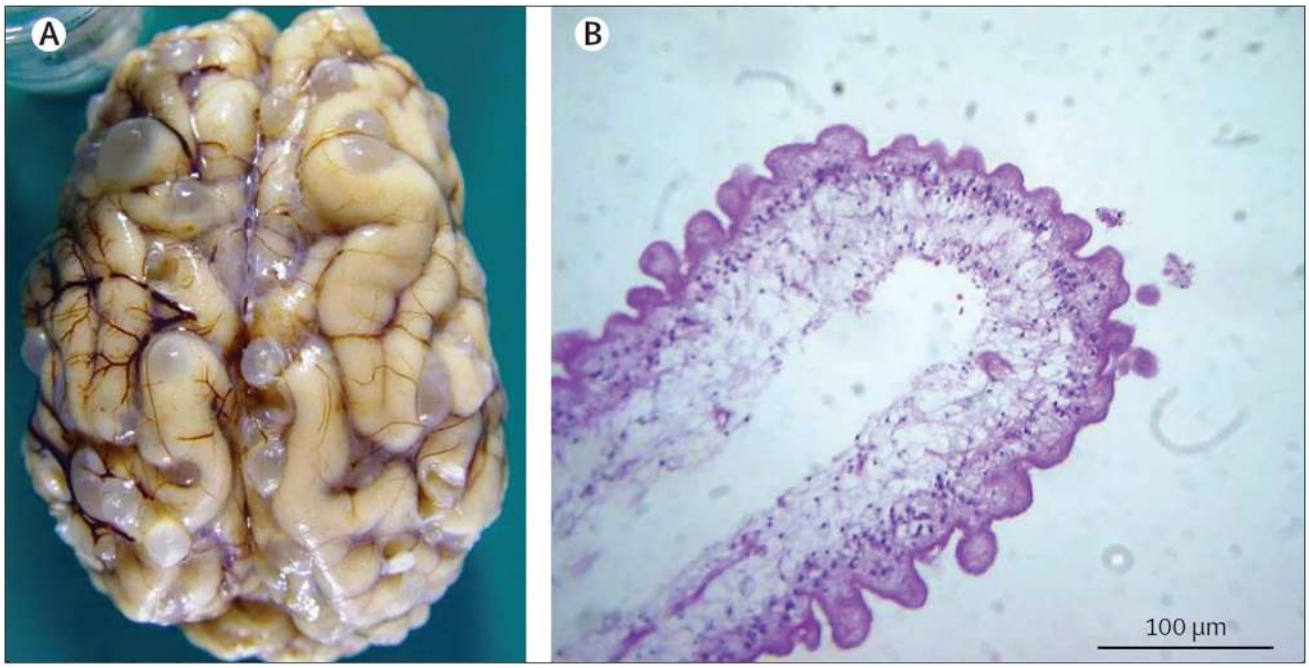

Figure 4: Pathology of cysticercosis

(A) Cerebral cysticercosis in a pig brain. (B) Typical cysticercal membrane (haematoxylin and eosin stain).

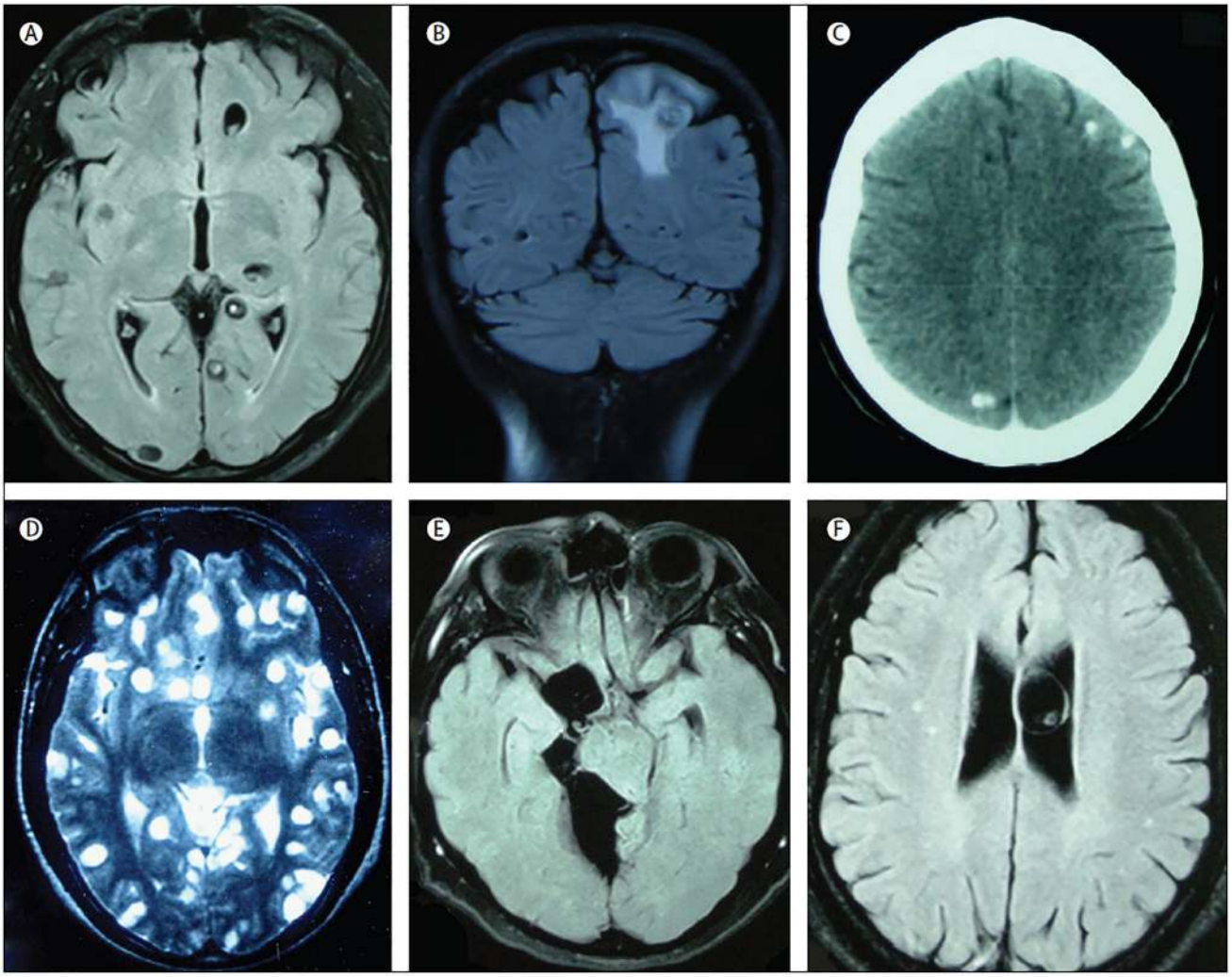

Figure 5: MRI imaging of human neurocysticercosis

Contrast used was gadoterate meglumine. Viable cysts in structural MRI (A); and enhancing nodule (B); many brain calcifications visible (C); massive parenchymal neurocysticercosis (D); basal subarachnoid neurocysticercosis (E); and intraventricular cysticercosis (F).

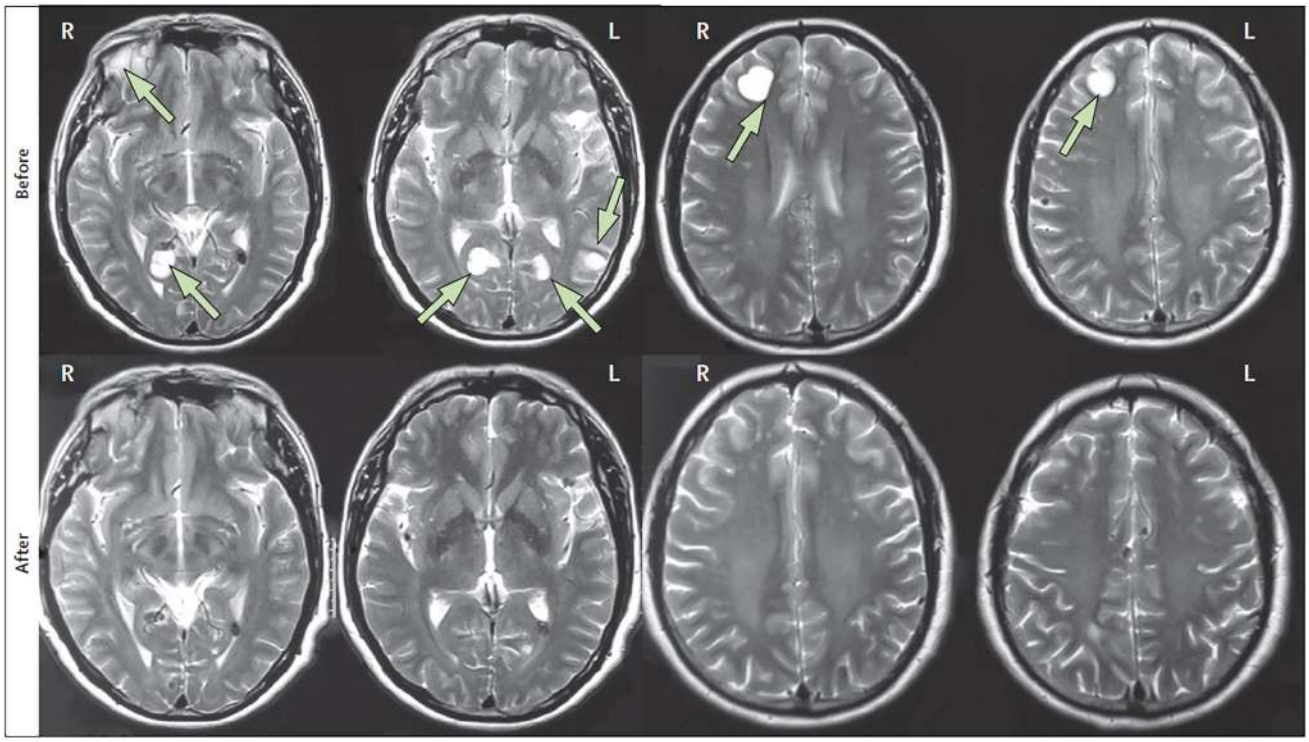

Figure 6: MRI scans before and after treatment in a patient with multicystic parenchymal neurocysticercosis

The patient was a 50-year old man who received 10 days of combined albendazole (15 mg/kg per day) plus praziquantel (50 mg/kg per day) standard treatment. The follow-up MRI was taken 6 months after treatment onset. Arrows show characteristic lesions of multicystic parenchymal neurocysticercosis.

Table:

Treatment approaches by type of neurocysticercosis

	Treatment approach
Extraparenchymal neurocysticercosis	
Basal subarachnoid neurocysticercosis	Prioritise control of intracranial hypertension; long term (1 month or longer) treatment with antiparasitic drugs with steroids *
Neurocysticercosis of the Sylvian fissure	Prioritise control of intracranial hypertension; long term (1 month or longer) treatment with antiparasitic drugs with steroids; * alternatively surgical excision
Intraventricular neurocysticercosis	Neuroendoscopical excision; consider third ventricle fenestration or placing a ventriculoperitoneal shunt, and post-surgery antiparasitic treatment; open surgery might be needed for fourth ventricle cysts
Small cysts in subarachnoid space of the convexity	Treat as parenchymal neurocysticercosis *
Intraparenchymal neurocysticercosis	
Cysticercotic encephalitis	Manage intracranial hypertension; do not use antiparasitic drugs
One or several cystic or degenerating lesions	Appropriate symptomatic management, including antiepileptic, analgesic, and anti-inflammatory drugs; antiparasitic treatment under hospital conditions with steroid treatment †
Calcified cysts only	Appropriate symptomatic management, including antiepileptic, analgesic, and anti-inflammatory drugs; for seizures relapses, repeat imaging looking for pericalcification oedema

* Treatment for small cysts in the brain convexity and length of steroid use are not based on randomised trial data.

† Outpatient-based antiparasitic treatment under appropriate monitoring could be considered in patients with a single enhancing lesion or those with a single small cyst.