Neurocysticercosis in Wisconsin: 3 Cases and a Review of the Literature

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ABSTRACT

Neurocysticercosis is the most common parasitic infection of the brain. Endemic in many regions of the world, neurocysticercosis is now showing up in nonendemic areas such as Wisconsin. We present 3 patients that illustrate features typical for neurocysticercosis in a non-endemic area, including immigrant/travel status, presentation with focal seizures, classic magnetic resonance imaging features of single enhancing lesions, and good response to treatment with anticonvulsants, anti-inflammatory agents, and cysticidal drugs. It behooves physicians involved in the care of at-risk populations to be aware of the clinical features, radiographic signs, diagnostic tests, and general principles for treating neurocysticercosis.

INTRODUCTION

Neurocysticercosis (NCC), the most common parasitic infection of the brain, is caused by ingestion of eggs the tapeworm *Taenia solium*.[1,2] NCC is endemic in the developing countries of Central America, South America, and parts of Africa and Asia, including India. NCC is a major cause of epilepsy in these endemic areas, where 25% to 40% of patients with new-onset epilepsy have evidence of NCC. At the same time, reported cases of NCC are increasing in the United States (especially in southwestern states) and other developed countries, especially among immigrants from endemic areas.[3] Here we report 3 cases of NCC that presented to our institution over the past few years, and review the epidemiology, life cycle, clinical presentation, diagnosis and treatment of NCC, to increase awareness of this disease among clinicians in nonendemic areas.

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CASE PRESENTATION

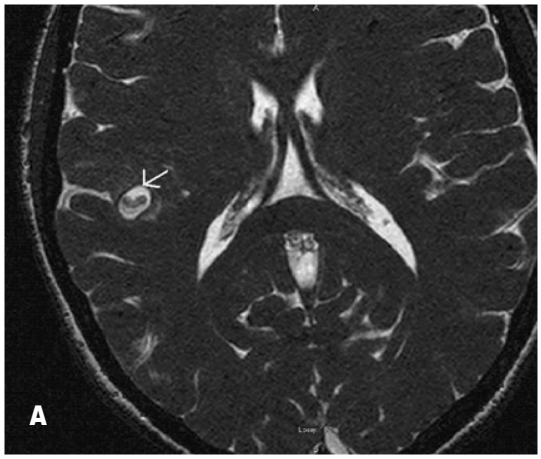
Patient 1

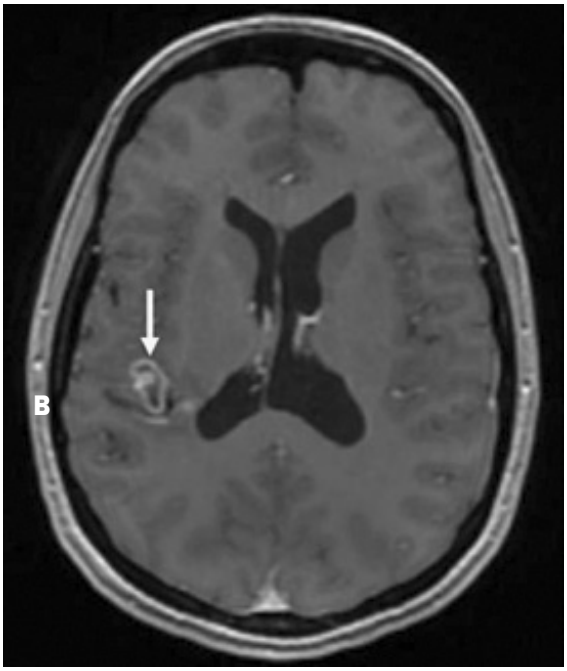
A 25-year-old woman presented with 3 focal seizures consisting of episodes of left jaw deviation and left eyelid and tongue twitching, plus chronic right-sided headache. She moved to Wisconsin from the Philippines 2 months prior to presentation. On examination, she had no focal neurological deficits. Brain magnetic resonance imaging (MRI) scan showed a 6 mm ring-enhancing lesion located superficially in the right frontal lobe adjacent to the motor strip. Electroencephalography (EEG) was unremarkable. Serum and cerebrospinal fluid (CSF) cysticercosis IgGs were negative by western blot of CSF and enzyme-linked immunosorbent assay (ELISA) of serum. The clinical diagnosis of NCC was highly suspected. The patient was given dexamethasone for 15 days followed by albendazole for 15 days. She also was started on levetiracetam for seizure prophylaxis. Two years later, she had an episode of left lip twitching after missing a few doses of levetiracetam. Otherwise, she has remained healthy and seizure free for the past 4 years. A follow-up MRI scan could not be obtained due to loss of insurance coverage.

Patient 2

A 38-year-old woman presented with intermittent left face, arm and leg dysesthesias, followed by a generalized tonic clonic seizure. She had moved from Mexico 14 years previously. On examination, there was decreased sharp perception on the left limbs with allodynia to cold and warm temperatures. At another facility, brain MRI scan showed a 16 x 8 mm ring-enhancing lesion in the right inferior frontal parietal area (Figure 1A). At the outside facility, a high suspicion for tumor resulted in 2 brain biopsies: one showed normal brain tissue and the second showed a mixed chronic inflammatory infiltrate with lymphocytes and eosinophils. When evaluated at our

Figure 1. Brain Magnetic Resonance Imaging Scans of Patients 2 and 3

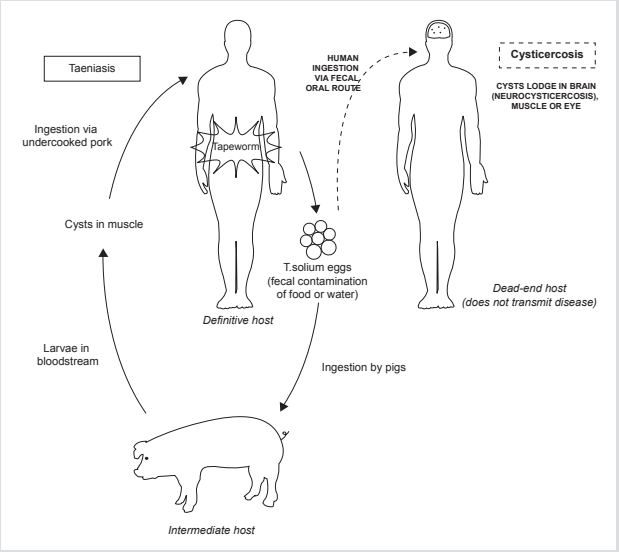




(A) Axial Sheath T1 with contrast of patient 2 showing ring-enhancing lesion with central T1 hypointensity in the right inferior frontal lobe. (B) Fast imaging employing steady state acquisition or FIESTA sequence of patient 3, showing sharply circumscribed cyst with complex internal structures (scolex).

hospital, NCC was suspected. Serum cysticercosis IgG was negative by ELISA. Per recommendation of an infectious disease consultant, she received a course of prednisone and 30 days of albendazole. Her dysesthesias were controlled by gabapentin and her seizures remain well controlled on lamotrigine 4 years after presentation. Follow-up brain MRI scan showed decreased size of the enhancing lesion.

Figure 2. Life Cycle of Pork Tapeworm, *Taenia solium*



Humans (definitive hosts) with adult tapeworm infection (taeniasis) excrete proglottids/eggs, which are ingested by pigs. Pigs (intermediate hosts) ingest tapeworm eggs or gravid proglottids from infected soil or vegetation. In pig intestine, eggs (oncospheres) hatch into larvae. Larvae invade intestinal mucosa, spread hematogenously to reach tissues such as muscle, brain, or eye, where they encyst as mature cysticerci. If eggs are ingested by humans via undercooked pork, they will get taeniasis – active tapeworm infection – completing the life cycle. Alternatively, humans can incur cysticercosis if they ingest tapeworm embryonated eggs via fecal-oral route. Oncospheres hatch in intestine, circulate to muscle, brain, or eye. In brain, larvae become cysts (cysterici), and the disease is called neurocysticercosis.

Patient 3

A 23-year-old woman presented with episodes of left arm dysesthesias described as "thousands of raindrops rushing up and down my left arm," sometimes ascending into her left neck and face, associated with numbness of the left arm and mild difficulty speaking and hearing. She also described chronic dull bilateral headaches for the year prior to presentation. She had traveled to Mexico multiple times, most recently 2 years prior. Her neurological examination was normal. Brain MRI scan showed a 9 x 12 mm ring-enhancing lesion in the right parietal lobe near the distal sylvian fissure with an internal soft tissue component within the cyst consistent with a scolex (Figure 1B). Cysticercosis serum IgG level by ELISA was 0.61 OD (>0.5 OD is considered positive). She was treated with prednisone and a 10-day course of albendazole, and was put on levetiracetam for seizure prophylaxis. She is doing well 8 years after initial presentation.

DISCUSSION

Epidemiology

In many areas of the world, NCC is endemic. In the United States, cases of NCC are increasing,[3,4] with estimates of about 1000 new cases annually.[5] NCC is not well known in Wisconsin,

Table 1. Diagnostic Criteria for Neurocystercosis[14]

Absolute Criteria
Histologic demonstration of parasite from biopsy of brain or spinal cord lesion
Cystic lesions showing scolex on CT or MRI
Direct visualization of subretinal parasites by fundoscopy
Major Criteria
Lesions highly suggestive of NCC by neuroimaging
Positive serum immunoblot for anticysticercal antibodies
Resolution of cystic lesions after therapy with albendazole or praziquantel
Spontaneous resolution of small single enhancing lesions
Minor Criteria
Lesions compatible with NCC by neuroimaging
Clinical manifestations suggestive of NCC
Positive CSF ELISA for anticysticercal antibodies or cysticercal antigens
Cysticercosis outside of CNS
Epidemiologic Criteria
Evidence of household contact with *T solium* infection
Individuals from areas where cysticercosis is endemic
History of frequent travel to disease-endemic areas

A definitive diagnosis requires 1 absolute or 2 major plus 1 minor and 1 epidemiologic criterion. A probable diagnosis requires 1 major plus 2 minor criteria, or 1 major plus 1 minor and 1 epidemiologic criterion, or 3 minor plus 1 epidemiologic criterion.
Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; NCC, neurocysticercosis; CSF, cerebrospinal fluid; ELISA, enzyme-linked immunosorbent assay; CNS, central nervous system; *T, Taenia*.

but as emphasized by our cases, health care professionals should be aware of this disorder. Of the 3 cases presented here, 2 patients are immigrants while the third patient is a Wisconsin native who traveled widely in endemic areas. A case of spinal intramedullary cysticercosis of the conus medullaris in an immigrant from Mexico previously was reported from our institution.[6]

Life cycle

The life cycle of the pork tapeworm *T. solium* is illustrated in Figure 2. Adult tapeworms consist of a scolex and numerous body segments called proglottids. The terminal proglottid contains thousands of eggs that are shed in carriers' stools. Cysticercosis is transmitted by the ingestion of *T. solium* eggs shed in the stools of a human tapeworm carrier (definitive host). Oncospheres (larvae or embryos) hatch in intestine of a pig or human that ingests them (intermediate hosts); the larvae invade the intestinal wall and disseminate hematogenously to other organs such as muscle and brain, where they mature into cysts (cysticerci) over several weeks. Cysticerci consist of a membranous wall filled with fluid and an invaginated scolex (head).

Humans who eat undercooked pork containing cysticerci can develop a tapeworm infection (taeniasis) but do not necessarily develop NCC. However, these individuals are at very high risk of autoinfection and resultant cysticercosis if they ingest tapeworm eggs through the fecal-oral route. Therefore, NCC is not acquired through eating undercooked pork but rather from oral-fecal transmission from definitive hosts shedding eggs in their stools. For example, an outbreak of NCC occurred in a non-endemic area of New York City when the parasite was transmitted by food workers (immigrants from endemic regions) infected with the tapeworm via the fecal-oral route.[7] Close contacts of a definitive host (who has taeniasis) are at risk for NCC. Humans with NCC (neurocysticercosis) are dead-end hosts and do not transmit the disease.

Clinical presentation

Clinical presentation of NCC varies depending on cyst localization, number, size, and stage. The most common presentation of NCC is seizures (75%),[8] followed by headaches (38%), focal deficits (16%), and signs of increased intracranial pressure (11%).[9] Up to 40% of new onset seizures in endemic regions are thought to be caused by NCC.[10] Seizures are typically focal but can secondarily generalize. The latency to presentation with seizures or other symptoms can be years. Focal seizures and dysesthesias were present in all of our patients.

NCC can be divided into 5 forms, according to the location of the lesion: parenchymatous, subarachnoid, intraventricular, spinal, and ophthalmic. Here we focus on the parenchymatous form, which is most common and affected each of our patients.

In the parenchymatous form of NCC, single or multiple cysticerci lodge in brain parenchyma as cysts or enhancing lesions. Three developmental stages of the cyst correspond to radiologic findings. First, the viable cyst stage consists of an invaginated scolex surrounded by translucent fluid and a membranous wall. There is little or no inflammation due to lack of host immune response, so minimal or no enhancement is observed on CT scan. The cyst may exist in asymptomatic form for months to years. The radiographic finding of a scolex within the cyst is pathognomonic for NCC.[11] In the degenerating cyst stage, fluid leaking from the cyst elicits an inflammatory response with enhancement on CT and MRI scans. Subsequently, further degeneration consists of larval decay, vesicle involution, and thickening of the vesicle wall. Finally, the calcified cyst stage comprises punctuate calcifications on CT scan and represents dead parasites.

Seizures are most likely to occur in the degenerating cyst stage, due to local direct pressure, inflammation, or edema, possibly exacerbated by a secreted substance such as cytokines that might alter ion channel function or network excitability.[12] Flares of edema surrounding otherwise inactive calcified lesions can also lead to seizures.[13]

Diagnosis

Diagnosis of NCC can be challenging, especially in nonendemic areas. History should emphasize residence in or travel to endemic areas in patients with an appropriate clinical presentation. Diagnostic guidelines for NCC are summarized in Table 1.[14]

Head CT scan is usually the first step in a diagnostic work-up.

The presence of a single enhancing lesion less than 20 mm, with a regular outline and no midline shift, is highly suspicious for NCC. CT findings change with developmental stage, as described above. MRI scans have higher resolution and can pick up small lesions, inflammation, and lesions adjacent to bone. Differential diagnosis of a single small enhancing lesion includes a primary or metastatic tumor, pyogenic or fungal brain abscess, toxoplasmosis, or tuberculoma.[15] It is critical to know the immune status of the patient in considering these possible etiologies. All of our patients were immunocompetent, human immunodeficiency virus (HIV) negative, and had not received a transplant.

Serology might be helpful when neuroimaging is nondiagnostic. Enzyme-linked immunoelectrotransfer blot (EITB) on serum is now the preferred laboratory method,[16] with a specificity of 100% and a sensitivity of 98% in patients with more than 1 cyst, though these values are lower in individuals with a single lesion; patients with only calcified lesions are often seronegative.[17] EITB is less widely available than ELISA, which has a lower diagnostic yield. Two of our patients were seronegative by ELISA and the diagnosis was suspected from clinical and radiologic findings. CSF studies are not helpful in most cases, though nonspecific abnormalities such as pleocytosis, elevated protein, and hypoglycorrachia have been reported.[18] Brain biopsy may offer a definite diagnosis but is not usually necessary. Of note, patient #2 underwent 2 brain biopsies searching for tumor, delaying the NCC diagnosis. This patient underscores the importance of recognizing the clinical signs and symptoms of NCC.

A reasonable diagnostic work-up for a patient presenting with a ring-enhancing lesion and seizures would include neuroimaging, EITB, toxoplasmosis serology, CSF gram stain and culture, HIV antibody testing, and tuberculosis testing. By the diagnostic criteria in Table 1, our patients #1 and #2 have probable NCC, while patient #3 has a definitive diagnosis. It is important to emphasize that although all of our cases had relatively good outcomes, NCC is not always benign, especially when multiple lesions are present.[2]

Treatment

The overall goals of NCC treatment are to prevent seizures, reduce inflammation, and reduce active cysts. A primary care provider can initiate an anticonvulsant drug and a neurologist can advise about subsequent treatment and drug discontinuation. The decision about cysticidal therapy is best made in consultation with an infectious diseases specialist.

Antiepileptic drugs

A patient with symptomatic NCC should be started promptly on an anticonvulsant. Seizures are usually controlled with a single agent. Phenytoin or carbamazepine is chosen most often, especially in developing countries, due to availability and low cost. Newer drugs such as levetiracetam or lamotrigine can be effective, as in our cases. Before tapering, some authorities recommend treatment for 2 years seizure-free or 6 to 12 months after radiographic resolution of viable/enhancing cysts. For children with a single small enhancing lesion, 1 year may be sufficient.[19] An abnormal CT scan with persistence of calcified lesions and an abnormal EEG are the most reliable predictors of seizure recurrence and should inform decisions about anticonvulsant tapering.

Anti-inflammatory treatment

Corticosteroids are used to decrease inflammation and edema, but a positive response is not pathognomonic as several etiologies of ring-enhancing cerebral lesion (see differential diagnosis above) may respond to steroids. Given the risk of exacerbating the host response after initiation of cysticidal therapy, corticosteroids are usually used as adjunctive therapy and should be given whenever cysticidal agents are used.[20] Steroids alone do not significantly improve outcome.[20,21] Treatment duration depends on disease burden.

Cysticidal agents

Accumulating data supports the use of cysticidal agents, especially in parenchymatous NCC, with the goal of treatment being elimination of active cysts. Recent evidence-based guidelines suggest that albendazole plus dexamethasone or prednisolone should be considered for patients with NCC, to reduce long-term seizure frequency and decrease the number of active lesions.[20,22] Concerns about the use of cysticidal agents include exacerbation of the inflammatory reaction causing more scarring and calcification, as well as uncertainty as to whether cysticidal agents alter the disease course. Of the two cysticidal agents most often used, albendazole and praziquantel, albendazole is better tolerated and interacts less with anticonvulsants.[23,24] There is no clear consensus about the duration of therapy, with 7 to 14 days vs 28 days shown to be equally effective. Patients with a large number of viable parenchymal lesions should be treated for a longer period. Treating single small enhancing lesions is controversial. Cysticidal drugs should not be used in patients with calcified lesions because the parasite is already dead. Again, consultation with an infectious diseases specialist is advised.

Prevention

As yet, there is no vaccine available for humans. Vaccination of pigs to control human *T solium* infection might be feasible. The mainstays of prevention are public awareness and education, careful hand hygiene, appropriate sanitation, and avoidance of undercooked pork and vegetables to reduce the prevalence of definitive hosts.[2]

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Quiz: Neurocysticercosis in Wisconsin: 3 Cases and a Review of the Literature

EDUCATIONAL OBJECTIVES

Upon completion of this activity, participants will be able to:

1. Raise awareness and index of suspicion of signs and symptoms of neurocysticercosis particularly in nonendemic areas.
2. Review the lifecycle of *Taenia solium* (tapeworm) with implications for preventive strategies.
3. Outline the components of a diagnostic workup for neurocysticercosis including absolute, major and minor criteria.
4. Summarize treatment strategies including the use of antiepileptic, anti-inflammatory and cysticidal agents.

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QUESTIONS

1. Which of the following is true?

   A. The most common presentation of neurocoystercosis (NCC) is seizures.

   B. Up to 40% of new onset seizures in endemic areas are due to NCC.

   C. Seizures are typically focal but can generalize.

   - ❑ A and B
   - ❑ A and C
   - ❑ All of the above

2. Which of these 3 diagnostic criteria fits the **absolute** criteria for neurocystercosis?
   - ❑ Positive serum immunoblot for anticysticercal antibodies.
   - ❑ Lesions highly suggestive of NCC by neuroimaging.
   - ❑ Cystic lesions showing scolex on CT or MRI.

3. Which is the preferred laboratory method for serum testing in suspected neurocystercosis?
   - ❑ EITB (enzyme-linked immunoelectrotransfer blot).
   - ❑ ELISA (enzyme-linked immunosorbent assay).

4. Humans who eat undercooked pork containing tapeworm cysts (cysticerci) can develop a tapeworm infection (taeniasis) but the ingestion of tapeworm eggs through the fecal-oral ingestion route is required to develop neurocysticercosis.
   - ❑ True
   - ❑ False

5. Of the two cysticdal agents used in treatment of neurocysticercosis which is better tolerated and interacts less with anticonvulsants?
   - ❑ Albendazole
   - ❑ Praziquantel

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