Subarachnoid Neurocysticercosis: Emerging concepts and treatment

Theodore E. Nash[1,*], **Elise M. O'Connell**[1]

[1]Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD

Abstract

Purpose of review: Subarachnoid neurocysticercosis (SUBNCC) is due to a morphologically unique proliferative form of *Taenia solium* involving the subarachnoid spaces. Prolonged therapy based upon the pathophysiology of SUBNCC and long-term follow-up have shed light on the course of disease and led to highly improved outcomes.

Recent findings: SUBNCC has a prolonged incubation period of between 10–25 years characterized by cyst proliferation and growth and invasion of contiguous spaces leading to mass effect(Stage 1). With induction of the host immune responses cysts degenerate leading to a predominately inflammatory arachnoiditis(Stage 2) causing hydrocephalus, infarcts and other inflammatory based neurological manifestations. Inactive disease(Stage 3) may occur naturally but mostly is a result of successful treatment, which generally requires prolonged intensive anthelminthic and anti-inflammatory treatments. CSF cestode antigen or cestode DNA falling to non-detectable levels predicts effective treatment. Prolonged treatment with extended follow-up has resulted in moderate disability and no mortality. Repeated short intensive 8-14- day courses of treatment are also used, but long-term outcomes and safety using this strategy are not reported.

Summary: SUBNCC gives rise to a chronic arachnoiditis. Its unique ability to proliferate and induce inflammatory responses requires long-term anthelmintic and anti-inflammatory medications.

Keywords

Neurocysticercosis; cysticercosis; cestode; biomarker; subarachnoid; brain inflammation; extraparenchymal

Introduction

Human infection

Neurocysticercosis (NCC) is an infection of the brain and spine with a larval form (cyst or metacestode) of the tapeworm *Taenia solium*. The pig is the usual intermediate host and is infected with larval cysts while humans are the definitive host and harbor tapeworms in the

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*corresponding author: Theodore E. Nash, M.D., Special Volunteer, Laboratory of Parasitic Diseases, 9000 Rockville Pike, Bldg 4, Rm 424, tnash@niaid.nih.gov, 301 496-6920.

small intestine. Similar to the pig, humans can also be infected and develop cysticercosis after ingestion of infectious ova shed in the feces of a human tapeworm carrier (fecal-oral transmission). In man, most cysts develop in the muscle, subcutaneous tissue, and brain but almost all the disease manifestations are due to infection involving the brain or spinal cord (neurocysticercosis)(1).

Disease manifestations based on location

The clinical manifestations of NCC vary considerably based on the number, location and involved brain compartment, size, presence and degree of inflammation and cyst form (1). Parenchymal infection most commonly causes seizures and/or epilepsy. Extraparenchymal disease is caused by infection of cysts located in the ventricular system or subarachnoid spaces (SUBNCC). Ventricular NCC usually presents with signs and symptoms related to obstructing cysts impeding CSF flow (hydrocephalus) and with frequently associated ventriculitis. The clinical presentation and initial approach to treatment is specific to ventricular NCC and differs from SUBNCC in most aspects(2).

Characterization of racemose and subarachnoid NCC

SUBNCC is caused by an anatomically abnormal, proliferative form of *T. solium* cyst (3) (4) (Figure 1, C–H) that is located within the subarachnoid spaces of the brain, most commonly the basilar cisterns, Sylvian fissures, and spinal cord(4). In contrast, normal *T. solium* cysts have a cysticercus cestode larval morphology characterized by a scolex invaginated into a fluid vesicle. These cysts are anlage of adult tapeworms (5) and can be found anywhere within the brain, but mostly occur within brain parenchyma, sulci or ventricles. Although sulci located cysts are within the subarachnoid space, in most aspects they resemble parenchymal cysts and are not classified as SUBNCC (4).

SUBNCC was first described by Virchow in 1860(6) who recognized grossly visible single or multicystic structures usually involving the base of the brain. However, Zenker in 1882 determined these were parasites and an unusual form of *T.solium* cysts {confirmed by recent molecular analysis(3)} after identification of cestode tegument and highly characteristic hooklets of *T.solium* within a sometimes present degenerated scolex. Zenker called this *Cysticercus racemosus* since the cystic structures resembled a bunch of grapes(7) (now commonly called racemose NCC) (Figure 1). Hennenberg in 1912(8) extensively reviewed the pathology and the pathophysiology of NCC. Even then, it was generally accepted that SUBNCC was caused by a proliferative form of *T. solium* manifested by unusual cystic growth with varying amounts of inflammation and fibrosis directed to residual degenerated parasite(9, 10) (11) (12). Although growth and proliferation of racemose forms have not been directly demonstrated in vitro, there is reasonable evidence indicating parasite growth (Table 1). It is the ability of this form of parasite to proliferate that gives rise to massive involvement and huge parasite burden, extensive and damaging subarachnoid located inflammation and the need for intensive prolonged or repeated treatments.

The Incubation period is decades

The incubation period is prolonged likely because of the slow growth of the parasite and accommodation of the subarachnoid space. Eventually the mass of the parasite becomes

large enough to cause mass effects and/or inflammatory caused symptoms ensue. After leaving an endemic area, patients with SUBNCC develop symptoms about a decade after immigrating to the U.S(11). However, a more realistic estimate that incorporates exposure before immigration yielded a median of 22.2 years(11), which agrees with the prolonged incubation period of the limited number of documented travelers(13), the minimal incubation period of about 11 years for extra-parenchymal NCC in immigrants evaluated and treated in a U.S. hospital(14) and the course of a U.S. immigrant diagnosed at age 17 with asymptomatic SUBNCC who was serially imaged but untreated until diagnosed with extensive SUBNCC 19 years later(11).

The course of disease before diagnosis is commonly prolonged and frequently punctuated with intermittent symptoms

In addition to the long asymptomatic incubation period, the course of disease following the initial symptom is commonly chronic, lasting over a decade, episodic, and typically unrecognized or undiagnosed(15) (11) (16) (17). This includes sometimes severe, relatively transient symptoms and signs that are frequently undiagnosed, cryptic or never came to medical attention. For instance, real life examples include undiagnosed lacunar infarcts that occurred years before the diagnosis of extensive SUBNCC(11) or a prolonged 20 year course of undiagnosed spinal meningitis due to spinal SUBNCC(18).

Clinical course following the diagnosis

There are multiple series describing the clinical manifestations (19) (20) (21), complications, and short-term treatments but no adequately detailed studies describing long-term follow up and outcome. The diagnosis is considered when a patient with exposure in an endemic area presents with severe headaches, hydrocephalus, loss of consciousness with imaging demonstrating one or more cystic masses within the subarachnoid spaces of the brain and/or spinal cord. The classic description is the appearance of a bunch of grapes, racemose NCC(7), which is visualized best by Magnetic Resonance Imaging (MRI) steady-state sequences (e.g. Balanced Fast Field Echo [bFFE], Fast Imaging Employing Steady-state Acquisition Cycled Phases [FIESTA], three-dimensional constructive interference in steady state [3D CISS]), but can often also be visualized with T2 weighted sequences. These masses may be so large that they cause mass effects resulting in death if undiagnosed or untreated(22). The sensitivity of enzyme linked immunotransfer blot (EITB) in serum approaches 100%, whereas CSF EITB positivity is highly specific for SUBNCC but not very sensitive(23).The cestode CSF antigen is almost always positive (24,11). Serum cestode antigen is commonly positive but is generally less sensitive than the CSF(25). In the absence of identifiable cystic structures the radiological features are less suggestive and require presence of other findings of NCC, positive blood serology for antibodies, or cestode antigen or DNA in the serum or CSF to suggest the diagnosis (11). CSF testing for *T. solium* antigen (TsAg) and *T. solium* DNA are both highly sensitive and specific, whereas these tests are less sensitive in the serum(11, 24) (25). There are increasing reports of the diagnosis being made through the use of metagenomic sequencing from the CSF(18).

Natural history of SUBNCC

Documentation of clinical history and imaging prior to and following the advent of clinical symptoms as well as the long-term follow up post treatment reveals a typical course of disease, which can be described along an overlapping continuum of three stages (11) and are summarized in Table 2 and illustrated in Figure 2. Stage 1 is characterized by the presence of multicystic structures occupying one or more subarachnoid spaces typically causing mass effect. Stage 2 is characterized by symptoms caused by an inflammatory arachnoiditis. Cystic structures can persist or regrow but are not the main drivers of clinical symptoms. Hydrocephalus, nerve entrapments, lacunar infarcts, long tract signs and symptoms and other manifestations develop during this stage. Occasionally the cystic components are small or not present. The MRI shows a diffuse or localized arachnoiditis; aseptic meningitis sometimes with focal symptoms is a common clinical presentation. Stage 3 disease is inactive disease, which can occur spontaneously or more commonly as a consequence of effective treatment (11). At this stage there is no viable parasite that can continue to grow, but *T. solium* antigen may persist to varying degrees. Evidence of prior disease including old lacunar infarcts, subarachnoid scarring, or calcifications are still present but parasitic cystic structures are absent and enhancement on MRI (a measure of inflammation) is limited, decreased or absent.

2Symptoms reflect the stage, location and extent of involvement. Patients with a giant cyst (Stage 1), which commonly originate from one of the Sylvian fissures or the basilar cisterns commonly present in extremis with mass effects or compress structures such as the optic nerve resulting in vision loss. There are various sequelae of the inflammatory process typical of Stage 2 disease. These include lacunar infarcts (26), less commonly large vessel infarcts (27), hydrocephalus frequently requiring a shunt for decompression, nerve entrapments, etc. Accompanying parenchymal or ventricular disease may give rise to characteristic symptoms. Neurological deficits that are present upon entry into Stage 3 are typically non-reversible.

Prolonged treatments lead to excellent clinical outcomes

There are no randomized trials of treatment and until recently no adequately detailed reports of long-term outcomes, which is required to adequately assess well documented propensity for recurrences. The anthelminthic drugs used, their duration and use of accompanying corticosteroids were based on the preferences of the treating physicians. There are a number of reports using intensive 8–14 day courses of treatment (28) (29) (30) (31) Many employ high dose albendazole and corticosteroids with a taper. Response is gauged by change in size of one of more cysts. Even though cysts decrease in size or disappear, many times surprisingly quickly, recurrences are common. Two reports found a single short course of albendazole led to a complete response in 25.8% of patients(30) and a 36% rate of recurrence after two treatment courses(21).In addition, degeneration of cysts and decrease in size or volume post treatment as assessed by MRI examinations is the most common and usually the only method used to determine the effectiveness of treatment in published studies. The high rate of recurrences despite total cyst degeneration but with persisting CSF abnormalities suggest use of MRI as a sole indicator of treatment efficacy is often misleading(32). Although it has been suggested repeated short courses of treatment are effective and lead to inactive disease(33) there are no published reports of long-term follow

up and clinical outcomes. Many patients with SUBNCC referred for treatment give a history of repeated failed courses of treatment of 8–30 days duration (11) suggesting prolonged treatment courses are required to prevent parasite regrowth and recurrence.

A recent paper employed long-term treatment with anthelmithics and anti-inflammatory agents to treat SUBNCC (11). The authors preferentially used combined albendazole and praziquantel, and employed high dosing of corticosteroids followed by a prolonged taper. To limit corticosteroid side effects, methotrexate and/or etanercept were added to the above regimen or used to in place of corticosteroids(11) (34) (35). There were prior studies that employed prolonged treatment courses. Proano et al. used this approach to treat unremoved 4th ventricular cysts(36) and later used it to treat giant subarachnoid cysts(22). In the recently published report, rather than treating for a specific duration, dose and level of immunosuppression, treatment decisions were made based upon multiple complimentary measures including decrease in cyst size and degree of enhancement by MRI, levels of CSF cestode antigen concentration, which reflects cyst burden and viability, and normalization of CSF pleocytosis. In general reassessments were scheduled every 3 months with evaluations earlier as required. Cestode antigen levels falling to undetectable predicted sustained inactive disease, likely cure. The use of CSF markers(37) (38) (32) and sometimes serum(39) to follow treatment response allowed an objective measure of effective treatment independent from change in cyst size, which even though a measure of treatment effect does not always predict cure. More recently, serial measurements of CSF *T. solium* DNA by qPCR were shown to be useful. Sensitivity to diagnose SUBNCC was about the same as cestode antigen and levels that became undetectable at least equally predicted inactive disease status or cure. Furthermore, this test may offer some predictive advantage (25). Since primers are more readily available than reagents for immune assays, this technique could be more readily available to treating physicians. A general drawback of prolonged and intensive therapy is the considerable increase in resources including medication and testing, invasive lumbar punctures, side effects of corticosteroid and expense. This highlights the need for randomized studies to determine the shortest and most effective treatments.

Role of inflammation and its control

Although the essential role of inflammation in disease pathogenesis was known over a century(8), the benefit and use of corticosteroids has never been studied(40) despite general agreement in the field of their usefulness to control inflammation in SUBNCC(23). Corticosteroids promptly alleviate symptoms and decrease enhancement, and symptoms and signs quickly return if corticosteroids are stopped too soon or the dose tapered too fast. However, the limitation and severity of corticosteroid side effects are well documented. More recently the empiric use of methotrexate(35) and etanercept (34) to control inflammation and limit corticosteroid side effects was reported. The potential efficacy of etanercept was supported by marked suppression of the usual proinflammatory cytokine release that occurs as a result of cysticidal treatment of naturally infected treated pigs(41). Since their use was found safe, likely beneficial and less morbid than corticosteroids, they were used as long as perceived necessary(34) and might have contributed to the limited morbidity reported. How to effectively and safely control inflammation remains one of the

most important unstudied aspects of treatment in SUBNCC and for that matter other forms of NCC as well.

Measures of treatment response and stage 3 SUBNCC

The presence of cestode antigen in the CSF in and serum of humans indicates infection with *T. solium*. In general prior studies suggest a decrease in levels in response to treatment is a measure of treatment efficacy(37) (42, 43). However, except in one instance(39) follow up was relatively short or not reported and the ultimate clinical state, e.g whether there were recurrences, of patients unknown. A recent study (11) found CSF analysis to be useful and the fall in cestode antigen to undetectable levels predicted sustained inactive disease(11). The long follow up period of many treated subjects highly suggested they were cured. Measurement of *T.solium* DNA in the CSF appears to be similarly helpful in diagnosis (38) (43) (38, 44–46) but also suffers from lack of long term follow up. However, the presence and change of CSF cestode DNA in SUBNCC were retrospectively evaluated in the long-term followed cohort noted above using a newly developed very sensitive qPCR(25). The assay was 100% sensitive in the CSF in detecting viable disease and 93.3% specific in reverting to negative in those with sustained inactive disease, likely cured. These quantitative assays appear are an objective measure of treatment efficacy and reappearance confirms recurrent infection and regrowth. They were useful as an endpoint of anthelminthic treatment.

Long term disease and clinical status

In contrast the general dismal clinical outcomes of reports of SUBNCC (47) (48), the recent series that employed long-term treatments and prolonged follow up had no deaths and moderate overall morbidity (11). Roughly a quarter of the patients ended up with significant morbidities but none required institutionalization and all were able to care for themselves. Although it is impossible to assign a specific factor that led to the outstanding clinical results compared to earlier studies since a number of practice changes were made, the use of prolonged anthelminthic drugs, effective control of inflammation, reliance of biological markers and MRI imaging to define efficacy, and close follow up all contributed.

Conclusion

Use of intensive prolonged anthelminthic and anti-inflammatory treatments guided by objective measures of treatment efficacy led to probable cures in most patients and markedly improved clinical outcomes. However, treatment was not standardized so it is unclear which changes led to improved outcomes. There are a number of outstanding questions. A clearer understanding of how the parasite proliferates should lead to ways to control its growth. Although inflammation results in most of the complications, how to best control inflammation has barely been discussed or studied. Also, more effective drugs or drug combination are desperately needed. Lastly, randomized trials are required to define the shortest, most effective and safest regimens.

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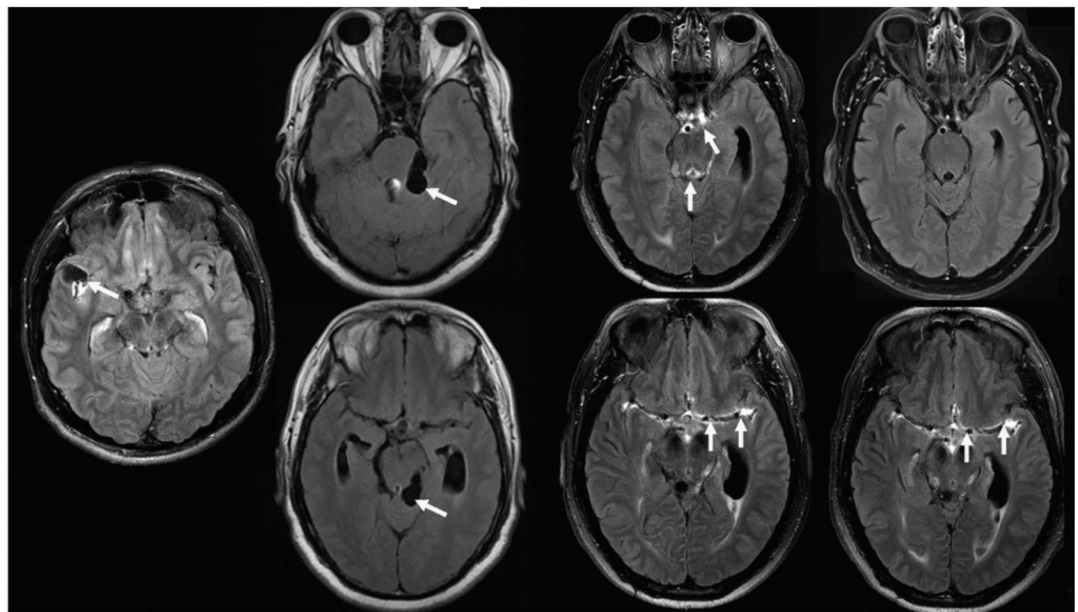
Main points

1. SUBNCC is an aberrant proliferative form of T. solium cysts that slowly grows and has a long incubation period lasting 1–2 decades as it expands mostly within the subarachnoid spaces.

2. Because the parasite proliferates, the mass of the parasite and antigen load can be enormous necessitating intensive long-term or treatments to kill all proliferating cells and intensive immunosuppression to control inflammation directed to large quantities of residual antigen.

3. Initial disease is caused by mass effects with varying but usually limited amounts of inflammation and then transitions into a mostly chronic arachnoiditis. Inflammation is the cause of most morbidity and mortality.

4. The disease course can be divided into overlapping stages of 1) mostly cystic masses with limited inflammation causing mass effects; 2) chronic arachnoiditis with inflammation directed to prior cysts and the presence of residual or regrown cystic masses and; 3) inactive disease but presence of inflammation caused sequelae.

5. Long term intensive cysticidal and immunosuppressive treatments to suppress inflammation guided by normalization of CSF parameters and cestode antigen levels resulted in improved outcomes including likely cures in all but one patient in the series, There were no deaths and moderate morbidity.
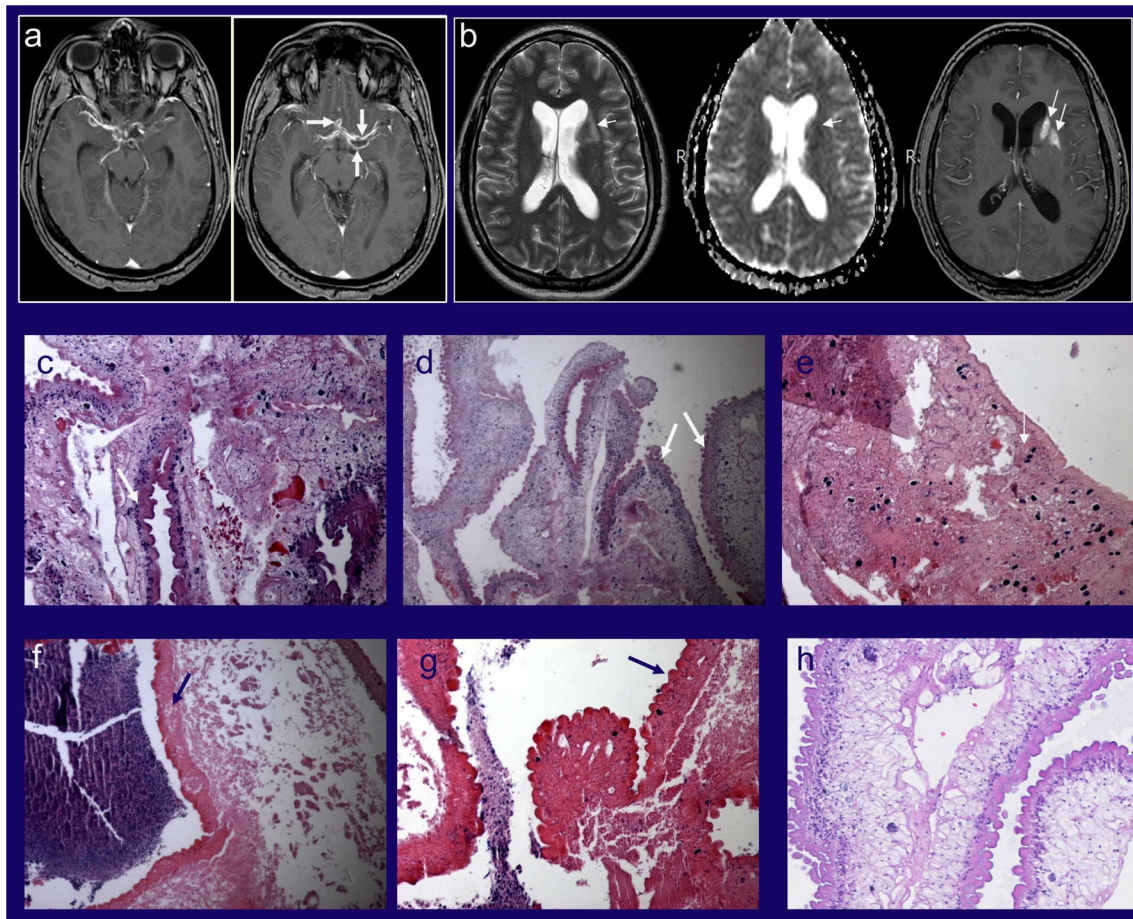
Figure 1. Radiology and histopathology of SUBNCC

MRI imaging before treatment of a patient who presented primarily with arachnoiditis and lacunar infarcts who underwent brain biopsy for diagnosis (Stage 2) (11). (A) Post contrast T1-weighted images showing abnormal enhancement along the courses of the middle and anterior cerebral arteries bilaterally with associated cystic changes (white arrows). (B) Axial T2, apparent diffusion coefficient maps and axial post contrast T1-weighted images showing subacute infarcts in the left basal ganglia and white matter (black arrows). (C-G) Various histopathology brain biopsy samples from the patient demonstrating variable morphologies of the racemose form. (C, D) Viable parasite with tegument (wide white arrows) showing disorganized growth and a variety and different types and arrangements of subtegumental tissue elements including amorphous substance, parasite cells and calcareous corpuscles better shown in (E) (narrow white arrow). (E-G) Degenerated but still recognizable cestode tissue with associated adjacent necrotic host response (hematoxylin staining amorphous material). (H) Histopathology from another patient with racemose cysts showing a different morphology that resembles the cyst wall, which lacks calcareous corpuscles that are found the neck of the cyst. The presence of viable and non-viable residual parasite in an untreated patient is expected and one cause of long-lasting subarachnoid inflammation.

Source: Panels A and B from reference 11.

	Pre-clinical	Stage 1	Stage 2	Stage 3
	Asymptomatic cystic proliferation, no obvious inflammation	Classic Racemose: Basilar cisterns and Sylvian fissure involvement of fluid-filled cystic masses, limited inflammation. Mass effect predominates	Arachnoiditis: Inflammation predominates with a spectrum of cyst damage or no discernible cyts	Cure: Decreased but persistent inflammation. Calcification and scarring seen
Parasite viability	+++	+++	+/-	-
TsAg and qPCR positivity	+/-	+++	+	-

Figure 2. Stages of subarachnoid neurocysticercosis

Post-contrast Fluid Attenuation Inversion Recovery (FLAIR) sequence Magnetic resonance imaging (MRI) images without gadolinium (Stage 1) and with gadolinium (Stages 2 and 3) are shown with pertinent findings highlighted by white arrows. The preclinical stage demonstrates an asymptomatic patient brought to medical attention after brain MRI following trauma showing cysts in the Sylvian fissure without surrounding enhancement or edema. Stages 1–3 show the same patient over the course of a 9-year period. Stage 1 shows bulky cysts in the quadrigeminal cistern causing mass effect but without enhancement or edema (not shown but evident in post gadolinium sequences). Stage 2 shows enhancement within the aqueduct (also had significant ventricular disease) and along the middle cerebral artery. Even at presentation there was significant enhancement along the middle cerebral arteries in gadolinium injected sequences. Commonly, different regions of brain have evolved at a slower or faster rate and are in a different Stage state. Pure Stage 1 with only cyst enlargement is not common, some inflammation is usually present. Stage 3 shows resolution of previous enhancement except along the middle cerebral artery. Parasite viability and *T. solium* antigen (TsAg) and qPCR positivity from the cerebral spinal fluid

(CSF) from each stage are also shown. This patient's course and imaging are detailed in reference 11.

Table 1

Evidence supporting racemose cysts proliferate

1	Extensive and massive involvement
2	Histopathology showing disordered growth, varied presence of parasite organelles and abnormal tissue organization
3	Presence of localized regions of growth (49)
4	Progressive growth and involvement over time in serially imaged untreated patients
5	Regrowth of cystic lesions after apparently effective treatment
6	Logical explanation for common asymptomatic spinal involvement due to seeding from basilar brain cysts (50)
7	Proliferation is a growth mechanism common to a number of cestodes (51)

Table 2

Stage progression of SUBNCC

Stage 1		
	a.	Closely fits original racemose NCC description
	b.	Base of brain and Sylvian fissure involvement common
	c.	Fluid filled cystic masses involving one or more subarachnoid spaces
	d.	Frequently untreated, first presentation, or remotely treated with regrowth
	e.	Symptoms and signs often related to mass effect
	f.	Inflammation (arachnoiditis) usually present but does not the predominate the disease pathophysiology. It may be contributing to symptoms and disease at this point.
	g.	CSF shows high cestode antigen and *T. solium* DNA, pleocytos is usually lymphocytic predominance, sometimes with increased eosinophils
Stage 2		
	a.	Inflammation dominates the pathophysiologic mechanisms
	b.	Cyst degeneration from treatment or natural evolution generates arachnoiditis directed to sites of degenerating (ed) cysts
	c.	The overall picture is one of inflammation in the presence of unaffected, partially affected, or fully degenerated cysts. At times, there may be an unexplained, localized or diffuse arachnoiditis without the presence of cysts
	d.	Lacunar infarcts are a major cause of morbidity
	e.	Hydrocephalus is frequent complication as is the development of localized signs and symptoms at sites of involvement
	f.	Decreased parasite mass leads to lower but still detectable cestode antigen and DNA levels; pleocytosis present sometimes with increased eosinophils
Stage 3		
	a.	Resolving or resolved disease, residual but decreasing inflammation as judged by decreased or no enhancement or decreased or no CSF pleocytosis
	b.	Sequelae of prior inflammation includes hydrocephalus, brain atrophy, residual of stroke, nerve entrapment, arachnoid cyst, calcifications within cisterns or following the middle cerebral arteries