Management of Neurocysticercosis in Children: Association of Child Neurology Consensus Guidelines

NAVEEN SANKHYAN,[1] RAZIA ADAM KADWA,[2] MAHESH KAMATE,[3] LAKSHMINARAYANAN KANNAN,[4] ATIN KUMAR,[5] GOURI RAO PASSI,[6] INDAR KUMAR SHARAWAT,[7] PRATIBHA SINGHI,[8] FOR ASSOCIATION OF CHILD NEUROLOGY DELPHI GROUP FOR NEUROCYSTICEROSIS IN CHILDHOOD*

From [1]Pediatric Neurology Unit, Department of Pediatrics, Post Graduate Institute of Medical Education and Research, Chandigarh; [2]Department of Pediatrics, Ankura Hospital for Women and Children, Hyderabad, Telangana; [3]Division of Pediatric Neurology, Department of Pediatrics, KAHER's Jawaharlal Nehru Medical College, Belagavi, Belgaum, Karnataka; [4]Gleneagles Global Hospital, Chennai, Tamil Nadu; [5]Department of Radiodiagnosis and Imaging, All India Institute of Medical Sciences, New Delhi; [6]Pediatric Neurology Division, Department of Pediatrics, Choithram Hospital and Research Centre, Indore, Madhya Pradesh; [7]Pediatric Neurology Division, Department of Pediatrics, All India Institute of Medical Sciences, Rishikesh, Uttarakhand; [8]Pediatric Neurology and Neurodevelopment, Medanta the Medicity, Gurugram, Haryana.

**List of group members provided as Annexure.*

Correspondence to: Prof Pratibha Singhi, Professor and Chief, Pediatric Neurology and Neurodevelopment, Medanta the Medicity, Gurugram, India. doctorpratibhasinghi@gmail.com

Justification: Neurocysticercosis (NCC) is a significant problem in India and other developing countries; however, several aspects of this disease have no clear, practical guidelines. There is a need for pragmatic guidelines, summarizing the available evidence, and filling in the gaps in evidence with expert advice to manage children with neurocysticercosis. **Process:** An expert group (16 members) and a writing group (8 members) was constituted, consisting of members with varied expertise. It included pediatric neurologists (18), neurologist (1), Neuroradiologists (4), and a parasitologist (1). The writing group divided the six topics and reviewed the literature on the topics individually to determine the clinical questions for which no clear guidance was available from the literature. The experts were then contacted and opinions were obtained online. The Delphi consensus method was adopted to arrive at a general consensus regarding various questions, with both the experts and the writing group members contributing. The final guidelines were then drafted by the writing group. **Recommendations:** Diagnosis of NCC should be based on clinical history and neuroimaging. Contrast-enhanced magnetic resonance imaging of the brain is the modality of choice. For single enhancing lesion, albendazole therapy for 10-14 days is recommended, and it should be combined with praziquantel for 10–14 days for more than one ring-enhancing lesions. For persistent lesion, the same dose and duration of albendazole or concurrent administration of albendazole and praziquantel should be given. Pulse intravenous steroids should be used to reduce the acute symptomatic edema in children with cysticercal encephalitis. Carbamazepine or oxcarbazepine are best suited for seizure prophylaxis for those who present with seizures; phenytoin and levetiracetam are the other alternatives. In the case of NCC presenting with symptoms other than seizures, there appears to be no role for routine anti-seizure medication prophylaxis. For a single ring-enhancing lesion, six months of anti-seizure medication is sufficient if the lesion resolves on follow-up. Those with persistent lesions, calcification, or multiple lesions, require a longer treatment duration of at least 24 months.

Keywords: *Cyst, Epilepsy, Parasitic infestation, Praziquantel, Seizures.*

Published online: August 02, 2021; ***PII:***S097475591600360

The World Health Organization (WHO) considers neurocysticercosis (NCC) as the most common preventable cause of epilepsy in the developing world. Neurocysticercosis accounts for an estimated 2 million people having epilepsy [1-4]. A study among people with active epilepsy found 34% to have NCC based on computed tomography and serology [5]. Around 17.3% of individuals had anticysticercus antibodies in a seroprevalence study conducted in Chandigarh [6]. A study conducted by the World Health Organisation on pig farmers of Uttar Pradesh showed a prevalence of teniasis in 18.6% of individuals, and around half of them had NCC [7]. A recent study showed a 4.5% prevalence of NCC in children attending tertiary care hospitals with acute focal neurological deficit or first episode of seizure [8]. In the Indian subcontinent; however, the spectrum of the disease seems to involve mostly young individuals with a single intraparenchymal cyst. The reason for this difference in clinical expression is unknown, although it could be related to less contact with tapeworm carriers, as similar patterns of disease are seen in people infected in regions where the disease is not endemic and in travelers [9].

Several aspects of this disease have no clear, practical guidelines. Infectious Diseases Society of America

(IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH) published a guideline intended to be applicable and feasible for developed nations (North America) [10]. These recommendations may not be applicable or feasible for developing countries like India, due to limited resources. Thus, there is a need for clear, pragmatic guidelines, summarizing the available evidence, and filling in the gaps in evidence with collated expert advice to manage children with NCC. To this end, the Association of Child Neurology took the initiative to get together experts to look at the evidence and bring forward a practice guideline to aid the management of children with neurocysticercosis.

OBJECTIVES

The guideline aims to provide directions for daily practice for the diagnosis and treatment of neurocysticercosis in children. The guideline not only looks at the up-to-date scientific evidence but also tempers it with expert advice to adapt to the Indian setting.

PROCESS

The writing group formulated six focus areas and several sub-questions, which aimed to cover all clinically relevant areas in diagnosing and managing neurocysticercosis in children. Within the major topics, several questions were shortlisted by the writing group to have further opinions and consensus among a broader range of experts. These included epidemiology, clinical features; Diagnosis: radiological tests, immunological tests, and other methods; antihelminthics: dose, duration, based on lesion load; management of NCC at atypical sites; steroids and anti-seizure drug use; and, statement on follow up, outcomes, and prevention **(Web Box I). Web Fig. 1** shows the constitution of the DELPHI group and the process followed.

The expert group and the writing group consisted of twenty-four members with varied expertise. It included 18 pediatric neurologists, 4 neuroradiologists, and one neurologist and parasitologist each. The 5-step Delphi process is outlined in **Web Fig. 1.** The writing group members then prepared the manuscript based on the relevant review of the literature and the results of the DELPHI consensus.

Quality of evidence scoring: The literature was selected by the committee members and was graded for quality based on the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) quality-of-evidence system [11]. The quality of articles to substantiate the conclusions by the group is provided with the concluding answer to each question.

Strength of recommendation assessment: On the basis of the selected literature and the online consensus development process, the group reached a consensus on a recommendation. The strength of the recommendation is expressed using the ESCMID strength of recommendation system [11], and many times does not always correlate with the quality of evidence. Hence, high quality of evidence may result in a marginal recommendation for use, while low-quality evidence may result in a strong recommendation for use.

RECOMMENDATIONS

Screening of Contacts

In view of the long incubation period between infection with NCC and the onset of symptoms, many of the tapeworm carriers who originally transmitted the infection may have cleared the intestinal infection or may no longer live near the patient [1,10,12]. Hence, stool examination for ova (which is the only available diagnostic test for tapeworms) is often negative in tapeworm carriers [13]. Even multiple examinations may not detect the tapeworm carrier. Even when ova are found, the morphology of the ova cannot distinguish *T. solium* from other taenia species. Thus, the yield of microscopy for the identification of tapeworm carriers is generally low, even in cases with apparent transmission outside of endemic areas [10]. Nevertheless, among patients who apparently acquired infection in the United States, tapeworms were documented in close contacts of 22% of NCC cases. Thus, most authorities would recommend screening for cases acquired outside endemic areas. Newer methods such as antigen detection in stool or detection of tapeworm-stage specific antibodies by immunoblot might improve the usefulness of screening, but these are presently only research techniques and not commercially available [10].

Recommendation

Routine screening of family members of children with NCC is not recommended. If at all screening is performed, fecal testing of the family for ova/cyst can be done.

Quality of evidence: 3; *Strength of recommendation*: D

Serological and Molecular Studies

The serologic antibody test of choice is the enzyme-linked immunoelectrotransfer blot (EITB) using parasite glycoproteins performed on serum. Enzyme-linked immunosorbent assay (ELISA) using crude antigens to detect antibodies are associated with frequent false-positive and false-negative results and should generally be avoided. Although EITB has 100% specificity and a sensitivity of 98% in patients with two or more cerebral

lesions, up to 50% of patients with a single brain lesion or with only calcified parasites may test negative [10]. The main problem related to ELISA on serum is the poor specificity, which is reported around 70% or less [14], compared with 86% for EITB [15]. The sensitivity of EITB varies with the form of NCC and specimen. In patients with multiple parenchymal, ventricular or subarachnoid NCC, the sensitivity of serum EITB is close to 100%. However, the sensitivity is poor in patients with a single parenchymal lesion or with only calcifications. Testing of serum is generally more sensitive than CSF using the EITB assay [16].

Antigen-based tests: They are also reported to be less sensitive than EITB. However, positive results correlate with the number of viable cysticerci. Parasite antigens are commonly detected in both serum and CSF in cases with multiple cysticerci such as subarachnoid NCC, and serial measurements may be helpful in the follow-up of complex cases [4].

Molecular tests: *T. solium* DNA has been detected by PCR or deep genomic sequencing using CSF of patients with subarachnoid NCC. However, there are no reports of its use in parenchymal NCC cases and its use may be even lesser in patients with a single brain lesion where most diagnostic problems arise. Cell-free *T. solium* DNA has been demonstrated in the urine and serum of patients with NCC, and recent data suggest that monocyte gene expression and serum mass spectrometry profiles could be used to identify NCC cases. To date; however, molecular biology assays are neither practical nor economical for routine case assessments. Techniques promoting amplification of DNA in a simple heating block or water bath may facilitate their application in resource-poor settings and include the loop-mediated isothermal amplification (LAMP) PCR [4].

Recommendation

The use of serological tests for diagnosis and clinical decision-making in children with NCC is not recommended.

Quality of evidence: 2; *Strength of recommendation*: D

Neuroimaging

Neuroimaging is established as a modality that can be used as an absolute diagnostic criterion for NCC [17]. The conclusive demonstration of a scolex within a cystic lesion on either computed tomography (CT) or magnetic resonance imaging (MRI) confirms the diagnosis of NCC **(Table I)**. The scolex is seen as a hyperdense dot within a cystic lesion on CT. It appears as hyperintense on T1-weighted images and hypointense on T2-weighted images on MRI. Sometimes other sequences of MRI are required to identify the scolex such as fluid attenuated inversion recovery (FLAIR), diffusion-weighted imaging (DWI), susceptibility-weighted imaging (SWI), or high-resolution heavily T2-weighted thin images including fast imaging employing steady-state acquisition (FIESTA), constructive interference in steady-state (CISS), or driven equilibrium (DRIVE). The typical appearance of the cyst is a less than 2 cm sized lesion with well-defined thin rounded walls located near the grey-white matter junction or basal ganglia. Other uncommon locations include the posterior fossa, subarachnoid spaces, intraventricular space, and spinal cord.

MRI plays a role in better characterization of the lesion by the demonstration of the scolex and internal characteristics. This further helps in differentiating NCC from its other close differentials, tuberculomas, and metastasis. The solid caseating tuberculomas characteristically have a T2 hypointense core which is not seen in any stage of NCC unless it is significantly calcified. It is one of the most helpful features in differentiating the two. Other features, though not specific, favouring a tuberculoma are a larger size (>2 cm), thicker and irregular walls, marked perilesional edema with mass effect, and associated basal meningitis. The presence of two-three conglomerate lesions may be seen in both entities and is not helpful in differentiation. On the other hand, some features suggest NCC over tuberculoma, such as intraventricular or subarachnoid location and multiple stages present simultaneously and pathognomonic features of individual lesions in case of multiple lesions [18].

MR spectroscopy of tuberculomas show elevated lipids and elevated choline/creatinine and choline/NAA ratios whereas these are not seen in NCC. On the other hand, NCC may show elevated acetate/succinate. Magnetisation transfer (MT) imaging has also been shown to be helpful in differentiating the two. The tuberculomas show a bright cellular component on T1-weighted MT images. The tuberculoma shows a hypointense centre with a hyperintense rim on T1-weighted MT images. The MT ratio of this hyperintense rim is significantly lower for tuberculomas compared to NCC and is due to the high lipid content in them [19,20].

MR also scores over CT for detection of lesions in atypical locations including intraventricular, subarachnoid, and intraspinal space. The high resolution heavily T2-weighted sequences are very useful in this. Even the lesions in the posterior fossa and those close to the skull are better delineated on MRI. Conglomerate lesions, subarachnoid or intraventricular lesions, and

Table I Clinical Features and Neuroimaging Appearance of Neurocysticercosis Based on Cyst Stage and Location

Cyst stage/location	*Clinical features*	*Neuroimaging characteristics*
Parenchymal		
Vesicular[a]	Usually asymptomatic	A thin-walled small CSF-like cyst with an eccentrically located scolex, no contrast enhancement of the cyst's wall, no surrounding tissue edema. The scolex can be iso-intensity or hyper-intensity on both T1-weighted and T2-weighted MR images and may show contrast enhancement.
Colloidal vesicular[a]	Seizures, focal neurological deficit, headache, vomiting, raised intracranial pressure, stroke, and rarely encephalitis	The cyst wall becomes thicker and irregular (late-stage) with contrast enhancement. The fluid within the cyst becomes slightly hyperintense on T1-weighted images and markedly hyperintense on T2-weighted or FLAIR sequences. Scolex decreases in size and eventually disappears. The surrounding tissue edema is striking.
Granular nodular[a]	Similar presentation as colloid vesicular	The cyst may be seen as a nodular or a thick, small, ring-like enhancement. Surrounding edema is not as extensive as the late colloidal vesicular stage and decreases gradually.
Nodular calcified	Focal or generalised seizures, headache, and vomiting.	Nodular calcifications <20 mm in diameter without surrounding edema or contrast enhancement.
Extra parenchymal		
Intraventricular	Commonly presents with acute obstructive hydrocephalus and raised intracranial pressure.	CSF-like cyst with or without scolex in the ventricular system, identified by the high signal intensity mural nodule, cyst wall outlined by cerebrospinal fluid in the ventricle on T1-weighted and FLAIR sequences. Commonly seen in the fourth ventricle, followed by the third, lateral ventricle, and aqueduct of Sylvius.
Subarachnoid	Communicating hydrocephalus, focal neurological deficit, nerve entrapments, thrombotic stroke, hemorrhage, lacunar infarctions, and raised ICP.	CSF-like cysts. Small in sulci, large in fissure or cistern, with a tendency to agglomerate, may cause mass effect and arachnoiditis.
Spinal	Myelopathy and radiculopathy are caused by spinal cord or root compression.	Cysts within the spinal subarachnoid space with or without evidence of inflammation/diffuse spinal arachnoiditis. Intramedullary cysts within the spinal cord.

[a]*Designated viable parenchymal cysts for the purpose of treatment.*

peripheral T2 hypointense ring with increased perfusion are the atypical neuroimaging of NCC [19].

Recommendation

MRI need not be done following CT in the following situations:

i) The CT conclusively demonstrates the presence of a scolex within the cyst; or

ii) In the absence of demonstration of scolex:

  a) If a solitary cystic/ring-enhancing lesion has all other typical sizes, shape, and location characteristics of NCC.

  b) Multiple lesions in different stages are present, including some cystic or ring enhancing or calcified.

Quality of evidence: 3; *Strength of recommendation*: D

MRI should be considered after CT in the following situations:

i) Atypical imaging features (conglomerate lesions, subarachnoid or intraventricular lesions) along with the absence of scolex;

ii) CT features create suspicion of intraventricular, subarachnoid, or intraspinal NCC; or

iii) Atypical clinical features including features of meningitis, encephalopathy, vision loss, fleeting headaches, stroke like features and behavioral changes.

Quality of evidence: 3; *Strength of recommendation*: B

Recommendation

If conventional MRI sequences have not been able to conclusively differentiate NCC from its differentials,

including tuberculoma, by failing to demonstrate scolex, then additional MR sequences may be acquired like MR spectroscopy and magnetization transfer imaging. However, the results of these may be used as supportive evidence rather than in isolation to differentiate the two.

Quality of evidence: 2; *Strength of recommendation*: B

Recommendation

Demonstration of scolex either on CT or MRI is the most conclusive evidence to differentiate between the two. In the absence of that, the features favoring NCC include a solitary well defined, thin-walled cystic or ring-enhancing lesion usually <2 cm in size with mild perilesional edema in a typical location of grey-white matter junction or basal ganglia. The presence of a T2 hypointense central core on MRI is strongly suggestive of tuberculoma over NCC in the absence of calcification as evidenced on CT or SWI sequences on MRI. The multicentricity of lesions with lesions showing different stages/features strongly favors NCC. Findings of MRS and MT imaging may be used as supportive evidence.

Quality of evidence: 2; *Strength of recommendation*: B

Recommendation

If the initial imaging (CT and/or MRI with recommended sequences when indicated) is not conclusive to differentiate NCC from tuberculoma, then a repeat contrast-enhanced MRI may be performed at an interval of 6-8 weeks to look for interval change. The imaging may be performed earlier if indicated by worsening or new clinical symptoms/signs.

Quality of evidence: 3; *Strength of recommendation*: C

Recommendation

The repeat imaging after treatment of NCC should be done at the interval of 6 months unless guided earlier by any worsening/new clinical symptoms/signs. This applies to both single and multiple NCC. MRI may be the preferred modality keeping into account the risk of radiation exposure with CT. The decision of administration of contrast may be left at the discretion of the radiologist, based on findings on plain MRI. A plain CT scan may sometimes be required after MRI if the presence of calcification is not conclusive on the MRI, and is required for clinical management.

Quality of evidence: 2; *Strength of recommendation*: B

Management of Intraparenchymal NCC

Albendazole therapy in solitary cysticercus granuloma (viable cyst, non-calcified): Cysticidal drugs hasten the resolution of NCC and improve the natural course of the disease. Cysticidal drugs have no role in treatment of calcified cysticercal granulomas. Both praziquantel and albendazole have cysticidal activity; however, a few studies have observed that treatment with praziquantel was less effective than albendazole in the complete cyst resolution and seizure control [21,22]. Praziquantel has more complex drug interactions with steroids, which are co-administered in NCC [23].

Albendazole with steroids should be considered for children with neurocysticercosis, to decrease the number of active lesions as well as to reduce seizure frequency. A short-course of albendazole treatment is as efficacious as four weeks treatment course in solitary cysticercus granuloma [24-27]. Monotherapy with albendazole is comparable to combination therapy of albendazole and praziquantel in the single solitary enhancing lesion in CT (SSECTL) [28].

Recommendation

The use of 10-14 days of albendazole therapy for all patients with single viable cyst is recommended.

Quality of evidence: 1; *Strength of recommendation*: B

Albendazole 15 mg/kg/day (maximum 1200 mg/day) in twice-daily doses should be given with meals. The quality of evidence is strong for use of albendazole but not for the duration of use.

Antihelminthic drugs for multiple viable cysts: Albendazole (ABZ) and praziquantel (PZQ) have different mechanisms of action, which may be beneficial when combined together in treating multiple NCC. Praziquantel is a pyrazinoisoquinoline derivative, of which the main pharmacological effects include muscle contractions, paralysis, and tegumentary damage, whereas albendazole is a benzimidazole, whose main mechanism of action is through selective degeneration of cytoplasmic microtubules resulting in energy depletion, disrupted cell division, and altered glucose intake.

Combination therapy with albendazole and praziquantel has been found to be safe and effective without any increase in adverse events. Increased serum albendazole concentrations were observed in patients receiving combination treatment compared with those receiving albendazole alone. Albendazole serum levels increased by 48% when given in combination with praziquantel [29]. Garcia, et al. [29] reported that combination of albendazole and praziquantel was associated with increased albendazole sulfoxide plasma concentrations. This along with a possible synergistic effect of two drugs may be beneficial for patients. A randomized trial of 32 pateints showed that the

combination therapy was more effective in destroying viable brain cysticercosis cysts than ABZ alone [30].

Combined treatment with albendazole and praziquantel was found to be superior in a three-arm randomized double-blinded study. One twenty-four patients (aged 16 to 65 years with 1 to 20 viable cysts) were randomly assigned to three arms (43 received standard dose albendazole; 40 received high dose (22.5 mg/kg/day) albendazole and 41 patients received combination therapy with standard dose albendazole and praziquantel). Complete cyst resolution in MRI brain performed 6 months after initial therapy was seen in 63% of patients who received combination therapy vs 73% and 83% resolution in the standard dose and high dose albendazole, respectively (P=0.141) in patients with one to two viable cysts. However, in patients with three or more then three cysts, complete cyst resolution was seen in 94% of patients who received combination therapy vs 21% and 48% resolution in the standard dose and high dose albendazole, respectively (P<0.001) [31]. Anti-helminthic drugs are not recommended in patients with cysticercal encephalitis or 'starry sky NCC' for fear of worsening the intracranial edema.

Recommendation

Albendazole (15 mg/kg/day) combined with praziquantel (50 mg/kg/day) for 10-14 days is recommended for more than two viable cyst.

Quality of evidence: 1; *Strength of recommendation*: B

Praziquantel dose at 50 mg/kg/day (upto 3600 mg/day), quality of evidence extrapolated from studies done in adult patients.

Treatment of persistent viable cysts: Response to a single course of cysticidal therapy is variable. A persistent cyst is seen in 30-40% of patients with a single viable lesion on follow-up. The persistence of the lesion is associated with seizure recurrence [32,33]. Rajashekar, et al. [32] treated 11 patients with persistent lesions with a repeat course of albendazole for two weeks. A significant reduction in cyst size was observed in two patients and complete resolution in two patients in follow-up CT scans. There are no randomized controlled trials or convincing data to suggest retreatment is better than symptomatic treatment; however, experts recommend retreatment [31]. Options for retreatment include a second course of albendazole or using the combination of albendazole and praziquantel.

Recommendation

There are two options to treat the persistent lesion. One is retreatment with the same dose and duration of albendazole and the second option is the concurrent administration of albendazole and praziquantel as for multiple lesion NCC.

Quality of evidence: 3; *Strength of recommendation*: C

Management of NCC at Atypical Sites

Cysticercal encephalitis: NCC can occur in atypical forms and at atypical sites in rare scenarios. The atypicality may be due to lesion load or due to the site. Rarely the NCC lesions can be in hundreds (miliary NCC) and can present with raised intracranial pressure due to edema associated with degeneration of numerous lesions simultaneously or sequentially [34]. In an even rarer situation, the intracranial lesions may be associated with disseminated lesions in other tissues of the body, primarily the muscles and subcutaneous tissue [35]. The literature on the management of cysticercal encephalitis is restricted to case reports. Due to the rarity of the presentation, there are no trials of drugs or other methods to manage these patients. There is; however, a consensus on avoiding the use of anti-helminthic drugs in these patients for fear of worsening the intracranial edema. Most experts and case reports suggest a beneficial effect of intravenous steroids in relieving the edema caused due to degeneration of cysticerci in cysticercal encephalitis.

The long-term management of cysticercal encephalitis is challenging, and the clinical course is often punctuated by recurrent episodes of symptomatic raised intracranial pressure and/or seizures.

Recommendation

Pulse intravenous steroids should be used to reduce the acute symptomatic edema in children with cysticercal encephalitis. The steroids suggested are methylprednisolone (10-30 mg/kg for 3-5 days; maximum 1000 mg/day) or dexamethasone (3-6 mg/kg/day for 3-5 days; maximum 16 mg/day).

Quality of evidence: 3; *Strength of recommendation*: A

Recommendation

Steroids can be used for long-term management of cysticercal encephalitis to prevent episodes of acute symptomatic cerebral edema in children with cysticercal encephalitis. Steroids in minimal doses and for the shortest possible period are suggested. Rapid tapering to the lowest effective dose and use of intermittent dose (e.g., alternate day) and monitoring for steroid side effects is suggested.The group does not support or recommend against the use of steroid-sparing drugs due to lack of evidence.

Quality of evidence: 3; *Strength of recommendation*: C

Subarachnoid, ventricular and spinal NCC: These varieties of NCC are exceedingly rare in children in the Indian sub-continent. Most of the reports on subarachnoid and ventricular cysticerci are from South-America [36,37]. Due to the rarity of the condition in India, and the availability of recent evidence-based guidelines published by IDSA and ASTMH [10], the group recommended that these guidelines may be adopted for these rarer kinds of NCC.

Steroids and Anti-Seizure Drug Use

Local inflammatory reaction surrounding NCC is widely prevalent as evidenced by worsening of clinical symptoms (e.g., headache), presence of perilesional edema and contrast enhancement on neuroimaging [38], and increased pleocytosis and elevated protein on serial CSF studies [39]. Host immune reaction to the degenerating cysts underly the pathophysiology of neuroinflammation in NCC. The resulting perilesional white-matter edema might occasionally produce focal neurological deficits and other devastating consequences due to mass effect and raised intracranial pressure. This is especially true when the cysts are located in the subarachnoid space, within the ventricles, orbit, brain stem, or the spinal cord. Thus, treatment with anti-inflammatory medications, particularly cortico-steroids is routinely considered in children with NCC.

In most observational and randomized controlled trials of NCC, patients were routinely treated with oral corticosteroids with or without the combination of anti-cysticercal treatment. Oral prednisolone has been used in doses ranging from 1-2 mg/kg/day for 3-10 days in most studies [40,41]. One meta-analysis, which included 13 studies with low-quality evidence, suggested that corticosteroids reduced seizure recurrence rate and hastened lesion resolution in the medium term (6-12 months) [42]. A recent meta-analysis found that the combination of albendazole with oral steroids provided superior seizure prevention and lesion resolution outcomes in cases of solitary cysticercus granulomas. But another meta-analysis concluded that corticosteroid treatment did not impact any outcomes significantly [43]. Thus, the available evidence is still conflicting about the effectiveness of a particular corticosteroid drug, dose, or duration of treatment in different stages of NCC.

Neuroimaging showing new-onset localized inflammation with perilesional edema and contrast enhancement in calcified NCC, years after the initial presentation, are well documented [44-46]. These cases present with seizures recurrences, headaches, or maybe asymptomatic [45]. The role of treatment with steroids in addition to anti-seizure prophylaxis in such cases is unclear. We do not recommend the routine use of steroids in such cases. Steroids might be considered in cases of large perilesional edema causing mass effect, midline shift, or other manifestations of raised ICT.

Recommendation

There is no role for routine use of steroids in cases of contrast-enhancing calcified NCC presenting with recurrence of seizures. Steroid use should be reserved for symptomatic cerebral edema.

Quality of evidence: 3; *Strength of recommendation*: D

Anti-Seizure Prophylaxis

As seizures are the most common presenting symptom, most patients with NCC receive anti-seizure medication (ASM) prophylaxis for varying durations depending on lesion resolution or calcification. Patients with calcified NCC receive long-duration ASM because of seizure recurrences after varying periods of seizure freedom, either on or off ASM. Though there is no high-quality evidence available to indicate the choice, dose, or duration of ASM in different NCC types, monotherapy with phenytoin and carbamazepine has been most commonly used [40], given the focal nature of epilepsy in this population. One pilot study demonstrated the safety, tolerability, and effectiveness of clobazam in NCC, but clobazam treatment was more expensive than phenytoin [47].

Recommendation

In the case of NCC presenting with other symptoms without seizures, there appears to be no role for routine anti-seizure medication prophylaxis.

Quality of evidence: 3; *Strength of recommendation*: D

Recommendation

Carbamazepine or oxcarbazepine are best suited for seizure prophylaxis in children with NCC in India. Phenytoin and Levetiracetam are other alternatives.

Quality of evidence: 3; *Strength of recommendation*: B

Epilepsy Surgery

Residual perilesional gliosis surrounding calcified NCC is thought to be responsible for long-term epilepsy [48]. Though most cases of epilepsy due to calcified NCC are controlled with ASM, a minority end up being drug-resistant. Surgical resection is one of the most effective curative treatment options available in cases of drug-resistant epilepsy due to calcified NCC. The pre-requisites for the surgical resection are that epilepsy

should be truly drug-resistant, seizures are frequent and disabling enough, clinical and video-EEG analysis proves that the calcified NCC is responsible for epilepsy and its removal is likely to cause seizure freedom. In endemic countries, calcified NCC's co-existence with hippocampal sclerosis (dual pathology) is well documented [49-53]. These patients are amenable to surgery, but the surgical strategy should be individualized. Patients with drug-resistant epilepsy should be referred early for consideration of epilepsy surgery.

Recommendation

Epilepsy surgery workup should be considered in children with NCC who failed two appropriately chosen ASM tried in optimal doses.

Quality of evidence: 3; *Strength of recommendation*: B

Optimal Duration of Anti-Seizure Medications

A review published in October, 2019 in the Cochrane Database of Systematic Reviews found four studies (466 patients) which addressed the question of duration of ASMs in patients with neurocysticercosis [54]. There was no difference in seizure recurrence in patients receiving anti-seizure drugs for 6, 12, or 24 months. The odds of seizure recurrence in six months treatment compared with 12 to 24 months treatment was not statistically significant [OR(95% CI) 1.34 (0.73 to 2.47); three studies, 360 participants, low certainty evidence]. When six to 12 months of therapy was compared with 24 months treatment, this too was not statistically significant [OR (95% CI) 1.36 (0.72 to 2.57); three studies, 385 participants; low certainty evidence].

Can the results of this analysis be extrapolated to children? Of the studies included in the analysis, one analyzed children between 3-14 years, one had only adults, one had both children and adults (age range 4-52 years), and the previous study did not clearly mention the age range [55-58]. All studies were single-center studies conducted in India. Notably, these studies excluded patients with persistent lesions, multiple NCC, and those needing albendazole therapy. The presence of calcified lesions was suggested to correlate with seizure recurrence and the need for prolonged therapy.

Two of these studies have suggested that the presence of calcification and persistence of the lesion on neuroimaging increases the risk of seizures and may require longer ASMs. A large prospective study of 185 patients (38.4% children <14 years) evaluated factors that predict seizure recurrence in patients with solitary cerebral cysticercosis granuloma when ASMs were withdrawn 3-12 weeks after cyst resolution on neuroimaging. Calcific residue on CT scan, breakthrough seizures, and a history of more than two seizures were found to be risk factors for recurrence on multivariate analysis [59].

Recommendation

For a single ring-enhancing lesion, six months of therapy anti-seizure medications is recommended if the lesion resolves on follow-up. Those with persistent lesions, calcification, or multiple lesions require a longer treatment duration of at least 24 months.

Quality of evidence: 2; *Strength of recommendation*: B

Recommendation

Anti-seizure medication may be withdrawn after 6 months if there is no calcific residue, there is resolution of cyst on neuroimaging, and the child has had less than three seizures in the past.

Children with evidence of calcification, persistent cyst, or a history of more than two seizures in the past may require a longer duration of therapy.

Quality of evidence: 2; *Strength of recommendation*: B

CONCLUSIONS

These guidelines are intended for pediatricians, neurologists, and family physicians, and reflect our approach to the management of the children with NCC based on the best available evidence in the literature and expert opinions.

Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*

Contributors: NS and PS: conceptualized the idea; NS, RAK, MK, LK, AK, GRP, IKS, PS: constituted the writing committee and drafted the manuscript; NS: devised and conducted Delphi process. All authors approved the final version of manuscript, and are accountable for all aspects of the manuscript.
Funding: None; *Competing interest*: None stated.

REFERENCES

1. Coyle CM, Mahanty S, Zunt JR, et al. Neurocysticercosis: Neglected but not forgotten. PLoS Negl Trop Dis. 2012;6:e1500.
2. Baird RA, Wiebe S, Zunt JR, et al. Evidence-based Guideline: Treatment of Parenchymal Neurocysticercosis: Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2013;80:1424-29.
3. Murthy JM, Subba Reddy YV. Prognosis of epilepsy associated with single CT enhancing lesion: a long term follow up study. J Neurol Sci. 1998;159:151-55.
4 Garcia HH, Gonzalez AE, Gilman RH. Taenia solium cysticercosis and its impact in neurological disease. Clin Microbiol Rev. 2020;33:e00085-19..
5. Rajshekhar V, Raghava MV, Prabhakaran V, et al. Active epilepsy as an index of burden of neurocysticercosis in Vellore district, India. Neurology. 2006;67:2135-39.
6. Khurana S, Aggarwal A, Malla N. Prevalence of anti-cysticercus antibodies in slum, rural and urban populations in and around

Union territory, Chandigarh. Indian J Pathol Microbiol. 2006;49:51-53.
7. Prasad KN, Prasad A, Gupta RK, et al. Prevalence and associated risk factors of Taenia solium taeniasis in a rural pig farming community of north India. Trans R Soc Trop Med Hyg. 2007;101:1241-47.
8. Kumar A, Mandal A, Sinha S, et al. Prevalence, response to cysticidal therapy, and risk factors for persistent seizure in Indian children with neurocysticercosis. Int J Pediatr. 2017;2017: 8983958.
9. Chandy MJ, Rajshekhar V, Prakash S, et al. Cysticercosis causing single, small CT lesions in Indian patients with seizures. Lancet. 1989;1:390-91.
10. White AC, Coyle CM, Rajshekhar V, et al. Diagnosis and Treatment of neurocysticercosis: 2017 Clinical practice guidelines by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH). Clin Infect Dis. 2018;66:e49-75.
11. van de Beek D, Cabellos C, Dzupova O, et al. ESCMID guideline: Diagnosis and treatment of acute bacterial meningitis. Clin Microbiol Infect. 2016;22:S37-62.
12. Gripper LB, Welburn SC. Neurocysticercosis infection and disease-A review. Acta Trop. 2017;166:218-24.
13. Sorvillo FJ, Waterman SH, Richards FO, Schantz PM. Cysticercosis surveillance: locally acquired and travel-related infections and detection of intestinal tapeworm carriers in Los Angeles County. Am J Trop Med Hyg. 1992;47:365-71.
14. Zammarchi L, Strohmeyer M, Bartalesi F, et al. Epidemiology and management of cysticercosis and Taenia solium taeniasis in Europe, systematic review 1990-2011. PloS One. 2013;8: e69537.
15. Proaño-Narvaez JV, Meza-Lucas A, Mata-Ruiz O, et al. Laboratory diagnosis of human neurocysticercosis: Double-blind comparison of enzyme-linked immunosorbent assay and electro-immunotransfer blot assay. J Clin Microbiol. 2002;40:2115-18.
16. Carod J-F, Randrianarison M, Razafimahefa J, et al. Evaluation of the performance of 5 commercialized enzyme immunoassays for the detection of Taenia solium antibodies and for the diagnosis of neurocysticercosis. Diagn Microbiol Infect Dis. 2012;72:85-89.
17. Del Brutto OH, Nash TE, White AC, et al. Revised diagnostic criteria for neurocysticercosis. J Neurol Sci. 2017;372:202-10.
18. Singhi P, Suthar R. Neurocysticercosis. Indian J Pediatr. 2015;82:166-71.
19. Pretell EJ, Martinot C, Garcia HH, et al. Differential diagnosis between cerebral tuberculosis and neurocysticercosis by magnetic resonance spectroscopy. J Comput Assist Tomogr. 2005;29:112-14.
20. Gupta RK, Jobanputra KJ, Yadav A. MR spectroscopy in brain infections. Neuroimaging Clin N Am. 2013;23:475-98.
21. Matthaiou DK, Panos G, Adamidi ES, Falagas ME. Albendazole versus praziquantel in the treatment of neurocysticercosis: A meta-analysis of comparative trials. PLoS Negl Trop Dis. 2008;2:e194.
22. Sotelo J, del Brutto OH, Penagos P, et al. Comparison of therapeutic regimen of anticysticercal drugs for parenchymal brain cysticercosis. J Neurol. 1990;237:69-72.
23. Romo ML, Carpio A, Kelvin EA. Routine drug and food interactions during antihelminthic treatment of neurocysticercosis: A reason for the variable efficacy of albendazole and praziquantel? J Clin Pharmacol. 2014;54:361-7.
24. Garcia HH, Gilman RH, Horton J, et al. Albendazole therapy for neurocysticercosis: A prospective double-blind trial comparing 7 versus 14 days of treatment. Cysticercosis Working Group in Peru. Neurology. 1997;48:1421-27.
25. Kaur P, Dhiman P, Dhawan N, et al. Comparison of 1 week versus 4 weeks of albendazole therapy in single small enhancing computed tomography lesion. Neurol India. 2010;58:560-64.
26. Sotelo J, Penagos P, Escobedo F, Del Brutto OH. Short course of albendazole therapy for neurocysticercosis. Arch Neurol. 1988;45:1130-33.
27. Singhi P, Dayal D, Khandelwal N. One week versus four weeks of albendazole therapy for neurocysticercosis in children: A randomized, placebo-controlled double blind trial. Pediatr Infect Dis J. 2003;22:268-72.
28. Kaur S, Singhi P, Singhi S, Khandelwal N. Combination therapy with albendazole and praziquantel versus albendazole alone in children with seizures and single lesion neurocysticercosis: A randomized, placebo-controlled double blind trial. Pediatr Infect Dis J. 2009;28:403-6.
29. Garcia HH, Lescano AG, Lanchote VL, et al. Pharmacokinetics of combined treatment with praziquantel and albendazole in neurocysticercosis. Br J Clin Pharmacol. 2011;72:77-84.
30. Garcia HH, Lescano AG, Gonzales I, et al. Cysticidal efficacy of combined treatment with praziquantel and albendazole for parenchymal brain cysticercosis. Clin Infect Dis 2016;62:1375-79.
31. Garcia HH, Gonzales I, Lescano AG, et al. Efficacy of combined antiparasitic therapy with praziquantel and albendazole for neurocysticercosis: A double-blind, randomised controlled trial. Lancet Infect Dis. 2014;14:687-95.
32. Rajshekhar V. Incidence and significance of adverse effects of albendazole therapy in patients with a persistent solitary cysticercus granuloma. Acta Neurol Scand. 1998;98:121-23.
33. Carpio A, Hauser WA. Prognosis for seizure recurrence in patients with newly diagnosed neurocysticercosis. Neurology. 2002;59:1730-34.
34. Singhi P, Saini AG. Pediatric neurocysticercosis: current challenges and future prospects. Pediatric Health Med Ther. 2016; 7:5-16.
35. Qavi A, Garg RK, Malhotra HS, et al. Disseminated cysticercosis: clinical spectrum, Toll-like receptor-4 gene polymorphisms and role of albendazole: A prospective follow-up of 60 cases with a review of 56 published cases. Medicine (Baltimore). 2016;95:e4882.
36. Amaral L, Maschietto M, Maschietto R, et al. Ununsual manifestations of neurocysticercosis in MR imaging: analysis of 172 cases. Arq Neuropsiquiatr. 2003;61:533-41.
37. Marcin Sierra M, Arroyo M, Cadena Torres M, et al. Extraparenchymal neurocysticercosis: Demographic, clinico-radiological, and inflammatory features. PLoS Negl Trop Dis. 2017;11:e0005646.
38. Gupta RK, Awasthi R, Rathore RKS, et al. Understanding epileptogenesis in calcified neurocysticercosis with perfusion MRI. Neurology. 2012;78:618-25.
39. Alarcón F, Escalante L, Dueñas G, et al. Neurocysticercosis. Short course of treatment with albendazole. Arch Neurol. 1989;46:1231-36.
40. Zhao BC, Jiang HY, Ma WY, et al. Albendazole and corticosteroids for the treatment of solitary cysticercus granuloma: A network meta-analysis. PLoS Negl Trop Dis. 2016;10:e0004418.
41. Mall RK, Agarwal A, Garg RK, et al. Short course of prednisolone in Indian patients with solitary cysticercus granuloma and new-onset seizures. Epilepsia. 2003;44:1397-401.
42. Cuello-García CA, Roldán-Benítez YM, Pérez-Gaxiola G. Corticosteroids for neurocysticercosis: A systematic review and meta-analysis of randomized controlled trials. Int J Infect Dis IJID Off Publ Int Soc Infect Dis. 2013;17:e583-92.
43. Otte WM, Singla M, Sander JW, Singh G. Drug therapy for

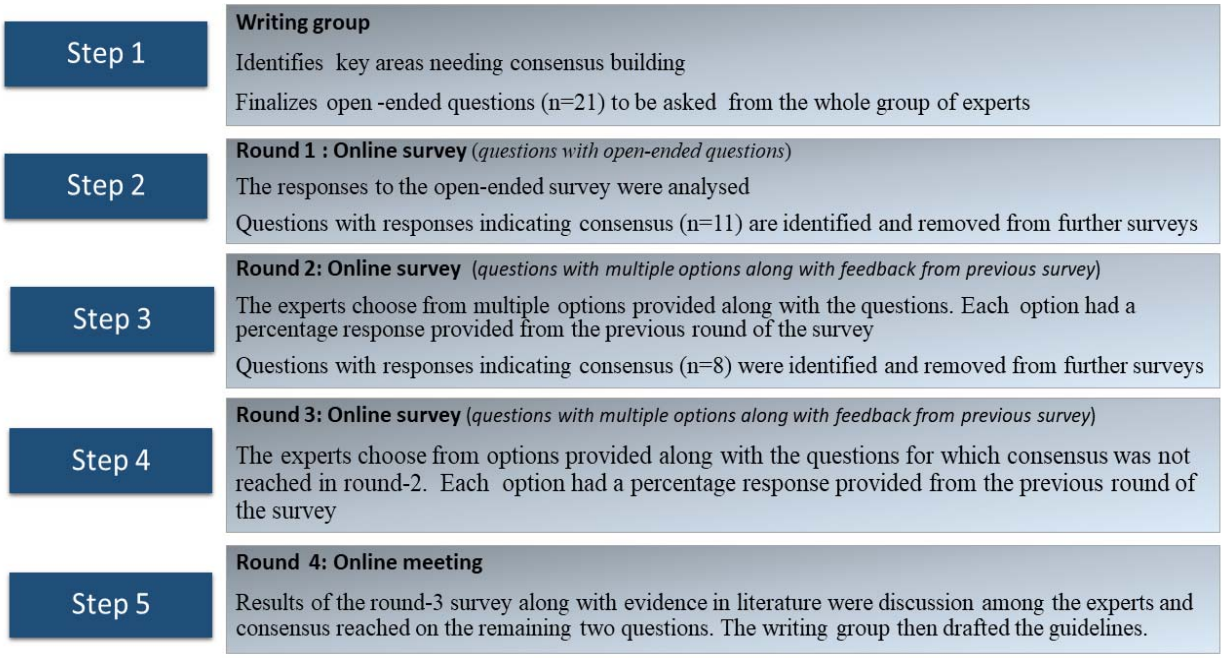
solitary cysticercus granuloma. Neurology. 2013;80:152-62.
44. Modak A, Suthar R, Sharawat IK, et al. An ambispective cohort study to assess seizure recurrences in children with calcified parenchymal neurocysticercosis. Am J Trop Med Hyg. 2019;101: 812-20.
45. Nash TE, Ware JM, Mahanty S. Natural history of patients with perilesional edema around taenia solium calcified granulomas. J Infect Dis. 2017;215:1141-47.
46. Nash TE, Pretell EJ, Lescano AG, et al. Perilesional brain oedema and seizure activity in patients with calcified neurocysticercosis: A prospective cohort and nested case-control study. Lancet Neurol. 2008;7:1099-105.
47. Kaushal S, Rani A, Chopra SC, Singh G. Safety and efficacy of clobazam versus phenytoin-sodium in the antiepileptic drug treatment of solitary cysticercus granulomas. Neurol India. 2006;54:157-60.
48. de Souza A, Nalini A, Kovoor JME, et al. Perilesional gliosis around solitary cerebral parenchymal cysticerci and long-term seizure outcome: A prospective study using serial magnetization transfer imaging. Epilepsia. 2011;52:1918-927.
49. Leite JP, Terra-Bustamante VC, Fernandes RM, et al. Calcified neurocysticercotic lesions and postsurgery seizure control in temporal lobe epilepsy. Neurology. 2000;55:1485-91.
50. Rathore C, Thomas B, Kesavadas C, Radhakrishnan K. Calcified neurocysticercosis lesions and hippocampal sclerosis: Potential dual pathology? Epilepsia. 2012;53:e60-62.
51. Rathore C, Thomas B, Kesavadas C, et al. Calcified neuro-cysticercosis lesions and antiepileptic drug-resistant epilepsy: A surgically remediable syndrome? Epilepsia. 2013;54:1815-22.
52. Singla M, Singh P, Kaushal S, et al. Hippocampal sclerosis in association with neurocysticercosis. Epileptic Disord. 2007;9: 292-299.
53. Bianchin MM, Velasco TR, Wichert-Ana L, et al. How frequent is the association of neurocysticercosis and mesial temporal lobe epilepsy with hippocampal sclerosis? Epilepsia. 2010; 51: 2359-60.
54. Sharma M, Singh T, Mathew A. Antiepileptic drugs for seizure control in people with neurocysticercosis. Cochrane Database Syst Rev. 2015;10:CD009027.
55. Singhi P, Ray M, Singhi S, Khandelwal N. Clinical spectrum of 500 children with neurocysticercosis and response to albenda-zole therapy. J Child Neurol. 2000;15:207-13.
56. Verma A, Misra S. Outcome of short-term antiepileptic treatment in patients with solitary cerebral cysticercus granuloma. Acta Neurol Scand. 2006;113:174-77.
57. Thussu A, Arora A, Prabhakar S, Lal V, Sawhney IMS. Acute symptomatic seizures due to single CT lesions: How long to treat with antiepileptic drugs? Neurol India. 2002;50:141-44.
58. Gupta M, Agarwal P, Khwaja GA, et al. Randomized prospective study of outcome of short term antiepileptic treatment in small single enhancing CT lesion in brain. Neurol India. 2002;50:145-47.
59. Rajshekhar V, Jeyaseelan L. Seizure outcome in patients with a solitary cerebral cysticercus granuloma. Neurology. 2004; 62:2236-40.

ANNEXURE

Participating Delphi Group Experts*

Rajni Farmania, *New Delhi*; Jatinder Singh Goraya, *Ludhiana, Punjab*; Vineet Bhushan Gupta, *New Delhi*; Rakesh Gupta, *Gurugram, Haryana;* Rakesh Jain, *Gurugram, Haryana*; Prashant Jauhari, *New Delhi;* Gurpreet Singh Kochar, *Ludhiana, Punjab*; Rashmi Kumar, *Lucknow, Uttar Pradesh*; Priyanka Madaan, *Chandigarh*; Abhishek Mewara, *Chandigarh;* Anita Sharma, *Gurugram, Haryana*; Lokesh Saini, *Jodhpur, Rajasthan*; Jitender Saini, *Bangalore, Karnataka*; Gangandeep Singh, *Ludhiana, Punjab*; Nitish Vora, *Ahmedabad, Gujarat*; Sameer Vyas, *Chandigarh*.

**Listed in alphabetical order.*



Web Fig. 1 Step followed in the DELPHI Process

Web Box I Step 1: Open-ended questions for experts

1. In your opinion/ experience, what are the common presenting symptoms of neurocysticercosis apart from seizures, in children?
2. What are the unusual or rare presentations of neurocysticercoses in children seen by you?
3. How in your opinion do symptoms of neurocysticercoses differ in children as compared to adults?
4. In your opinion, should we screen family members of a child presenting with neurocysticercosis? If so how?
5. Do you use serological tests for the diagnosis of neurocysticercosis? If yes in what situation and what test?
6. In your opinion, when will you order an MRI in a child suspected of NCC, who has already had a CT done?
7. What are the special techniques in MRI to help detect NCC and to differentiate from other close differentials? (*Question specifically for experts in radiodiagnosis*)
8. In your opinion, which findings do you rely on to reliably differentiate NCC from tuberculoma radiologically? (*Question specifically for experts in radiodiagnosis*)
9. What in your opinion should be the ideal time to repeat the imaging after treatment of NCC, does it differ in those with one versus those with multiple lesions? Secondly do you order a CT or MRI? Plain or contrast?
10. In case initial imaging is not conclusive to differentiate NCC from tuberculoma, what in your opinion is the role of repeat imaging and to be done at what interval?
11. What is your preferred way to treat ring enhancing lesions that persist after one course of antihelmenthics? Concurrent administration of albendazole and praziquantel OR a longer duration of albendazole OR repeat course of albendazole in same dose OR any other option?
12. In children who do not have seizures but have NCC detected on neuroimaging (e.g., imaged for evaluation of headache). Will you use the following?
    a. Antihelmenthic drugs
    b. Antiseizure medications
13. In your opinion what is the optimal duration of Albendazole in Solitary cysticercus granuloma –one week, two weeks or 4 weeks regimen?
14. What is your preferred way to use antihelminthic drugs for more than two ring enhancing lesions (Not encephalitis) ? Concurrent administration of albendazole and praziquantel OR a longer duration of albendazole OR any other option?
15. What, in your opinion, is the best drug to manage NCC encephalitis with **acute symptomatic** cerebral edema in children (headache, vomiting, behaviour change, papilledema, reduced sensorial level)? Notably, the role of steroid pulses/oral. (which steroid and for how long?
16. What, in your opinion, is the best drug for **long term management of NCC encephalitis** with symptomatic cerebral edema (intermittent headache, vomiting, behaviour change, persistent papilledema)? Notably, the role of steroids and steroid sparing agents
17. Subarachnoid and ventricular cysts are rare in children and in the Indian sub-continent. They are more common in series from the South-America. Evidence based guidelines published by IDSA and ASTMH may be adopted for India for these rarer kinds of NCC.[1] Are you in agreement with this?
18. What anti-seizure drug, dose and duration of therapy would be best suited, as per your practice, in the following situations?
    a. Single ring enhancing lesion
    b. Multiple ring enhancing lesions
    c. Calcified NCC
19. When do you consider epilepsy surgery for calcified NCC?
20. In your opinion what is the treatment of calcified lesions that show edema along with seizures? –would you use antihelminthic drugs and/or anti-inflammatory drugs> which drug do you prefer and the dose/duration you follow.?
21. What is the optimal duration for treatment with antiepileptic drugs in children with NCC and on what criteria must we base our decision to withdraw anti-seizure drug?

[1] Diagnosis and Treatment of Neurocysticercosis: 2017 Clinical Practice Guidelines by the Infectious Diseases Society of America (**IDSA**) and the American Society of Tropical Medicine and Hygiene (ASTMH). White AC Jr, Coyle CM, Rajshekhar V, Singh G, Hauser WA, Mohanty A, Garcia HH, Nash TE. Am J Trop Med Hyg. 2018 Apr;98(4):945-966.