

Radiological screening for neurocysticercosis in asymptomatic siblings of children with neurocysticercosis: An observational cohort study

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ABSTRACT

Introduction: Neurocysticercosis (NCC) is the most common helminthic infection of the central nervous system and a leading cause of acquired epilepsy worldwide. Tuberculosis (TB) is transmitted through droplet infection to index pediatric case from only sputum acid-fast bacilli -positive patients while NCC in an index child can result from fecal–oral route from other family members who are *Taenia* carriers or through autoinfection as well. **Objective:** Similar to universal practice of TB screening of asymptomatic family members with chest X-ray which poses radiation hazard, radiation-free radiological screening by magnetic resonance imaging (MRI) brain of asymptomatic siblings of children with NCC was carried out in the present study in addition to evaluation of family members for taeniasis. **Methods:** Siblings (between 1 and 18 years of age) of children attending the pediatric NCC clinic at a tertiary care hospital in Chandigarh, India, with clinically suspected and radiologically confirmed the diagnosis of NCC, were enrolled. Contrast-enhanced MRI brain was obtained free of cost to detect the presence of asymptomatic NCC in siblings enrolled in the study. Stool analysis of family members of children with NCC was carried out to detect *Taenia solium* carriers. **Results:** Of 39 enrolled asymptomatic siblings, 4 (10.3%) children were detected to have solitary intraparenchymal NCC lesion. Of the aforementioned four siblings, 3 (75%) had viable lesions, while 1 (25%) had calcified lesion. Only 2 (1.7%) of 118 stool samples of family members tested were positive for *T. solium* eggs. **Conclusions:** The results from the present study suggest clustering of NCC cases in the family and that majority of children with NCC may continue to remain asymptomatic. Targeted family screening for NCC in asymptomatic family members of children with NCC may prove more cost effective than routine mass screening. Based on the results of this study, targeted deworming of community food handlers and caution in conducting routine deworming of children are suggested.

Key words: Cognitive impairment, Deworming, Epilepsy, Neurocysticercosis, Screening, Taeniasis

In the usual life cycle, ingestion of improperly cooked pork with cysts leads to the entry of tapeworm in the intestine of carriers. The tapeworm is highly infectious and stools of taenia carriers may contain several proglottids in a day with each proglottid containing upto 30,000 infectious eggs. In places lacking appropriate sanitation, pigs access and ingest these contaminated stools, become infected with tapeworm eggs, and develop cystic larvae in their flesh and other tissues (porcine cysticercosis). However, humans are exposed to tapeworm eggs by microscopic fecal contamination, resulting in cysticercosis and not by ingesting pig meat containing cysts. Thus, in non-cysticercosis endemic regions, humans can still develop cysticercosis by infection from *Taenia* carriers as well as by autoinfection by fecal–oral route [1-4].

Tuberculosis (TB) is transmitted through droplet infection to children from sputum Acid Fast Bacilli -positive patients only, while Neurocysticercosis (NCC) in a child can result from transmission through fecal–oral route from other family members who are *Taenia* carriers or through autoinfection as well if child is

a *Taenia* carrier. Moreover, due to common food handler at home or commercial place (eating joint, raw food supplier, etc.) from which food is procured by family members, clustering of cases of taeniasis and/or NCC is quite possible. Similar to screening for TB of family members of index pediatric TB case, screening family members for taeniasis may prove beneficial in children with NCC if clustering of NCC cases is seen in family members. Based on the aforementioned hypothesis, the present study was planned to determine the prevalence of NCC among asymptomatic siblings of children with NCC and taeniasis in family members of children with NCC. However, unlike the practice of routine screening of asymptomatic family members of pediatric TB patients with chest X-ray which poses radiation hazard, screening of asymptomatic siblings of children with NCC with MRI posing no radiation hazard was carried out in the present study. To the best of our knowledge, no study reporting on radiological screening of asymptomatic siblings of children with NCC has been published till date.

MATERIALS AND METHODS

This was a prospective observational cohort study, in which a total of 39 asymptomatic siblings of children with NCC registered in pediatric NCC clinic of our institute were enrolled. The number of enrolled cases was restricted due to the study being a funded study by the Department of Science and Technology, Chandigarh. All the consecutive children attending the pediatric NCC clinic during follow-up visit whose parents consented to enrollment of their asymptomatic children (siblings of NCC cases) under 18 years of age were enrolled. Ethical approval for the study was received from the Institutional Ethics Committee.

We included the symptomatic siblings of children with NCC after getting informed consent/assent from parents/guardian and child. The patients, who have received cysticidal therapy in the past 6 months as a part of routine deworming, and the patients whose parents declined to give consent for the study were excluded from the study.

Parents of children with NCC were explained about greater risk of NCC in their other children(s) than general population. They were detailed about the study protocol and investigations that shall be carried out in case they consented to enroll. Contrast-enhanced MRI brain was carried out to detect the presence of asymptomatic NCC in siblings free of cost as this was a funded study by the Department of Science and Technology, UT Chandigarh. No computed tomography (CT) scans which pose radiation hazard to participants were undertaken. Stool samples of all consenting family members (parents and/or siblings) of all the enrolled children were evaluated for the presence of *Taenia* eggs.

All the enrolled patients were followed regularly for at least 6 months. *Taenia* carriers were treated. Children with asymptomatic NCC were counseled regarding high risk of seizure(s) in future and need for regular follow-up. In addition, they were advised against routine use of cysticidal therapy for deworming as in the absence of steroid cover and medical supervision as seizure(s) may get precipitated. Clinical outcome was recorded as the occurrence of seizures based on reports from patients/guardians at each follow-up visit.

RESULTS

Of 39 enrolled asymptomatic siblings, 56.4% were males with mean age of 9.6 years (range 3–17 years). Four (10.3%) children were detected to have solitary intraparenchymal NCC lesion (Table 1). Of the aforementioned four siblings, 3 (75%) had viable lesions, while 1 (25%) had calcified lesion (Figs. 1–4). One of these three children with viable NCC lesion had unprovoked focal

onset seizure during follow-up and was started on antiepileptic drugs, enrolled in NCC clinic, and received cysticidal therapy. Only 2 (1.7%) of 118 stool samples tested were positive for *Taenia solium* eggs.

DISCUSSION

NCC is a neglected tropical disease which causes high morbidity and mortality. It is a major infectious cause of epilepsy globally and, especially, in developing countries like India [5,6]. A meta-analysis revealed that brain lesions, due to NCC, are present in approximately 29.0% (95% UI 22.9%–35.5%) of people with epilepsy in populations living in *T. solium* endemic areas in settings with poor sanitation and pig management practices and where pork is consumed [7]. In a recent meta-analysis and systematic review of central nervous system infections by Robertson *et al.*, six WHO regions were included, with 14 studies from Latin America, four from the US/Canada, three each from Southeast Asia and Africa, two from the Eastern Mediterranean, and one from Europe. The overall estimate of the global population affected by NCC was 24,743,893 people each year. The incidence of NCC in Southeast Asian Region of the WHO was reported to be 436/100,000 population [8]. In a community-based study involving 2415 residents of Atahualpa, Ecuador, a NCC prevalence rate of 9.9/1000 based on CT scan evaluation was reported [9]. Similar study involving 2273 residents of an Ecuadorian rural community reported the prevalence rate of active epilepsy as 11.4/1000 and NCC was detected through CT scan examination in 53.8% of the cases with active epilepsy [10]. Raina *et al.* reported point prevalence of NCC as 11.31/1000 in a study using neuroepidemiological and neuroimaging procedures to assess the prevalence of NCC on community-based approach conducted on 2209 individuals of six villages of Chattah zone of Jammu district. The prevalence ratio for men was more than double in comparison to women [11]. Prevalence rate of NCC as a cause for epilepsy in a study conducted in Kashmir Valley (Jammu and Kashmir) was markedly lower (2.47/1000) than the reported prevalence from Jammu district and was attributed to no pork consumption for religious reasons in Kashmir Valley, making the area free of human taeniasis, which is a cause for the development of NCC [12]. In a study in Uttaranchal region of India on patients reporting to hospitals, 3.94% of 15,000 patients screened showed NCC. Most of them presented with generalized seizures (62.5%), and the rest had headache (37.5%), focal seizures (20.8%), localizing neurological signs (16.6%), meningitis (4.1%), and dementia (1.3%). On neuroimaging, parenchymal lesions were most prevalent (81%) while interventricular lesions were also not very uncommon (32%). Most of them had single lesions

Table 1: NCC lesion characteristics picked up on screening in asymptomatic children

Age (year)/Sex	NCC Stage	Location of lesion	Contrast enhancement	Perilesional edema	Calcification
17/Female	Granular nodular	Right frontal	Yes	No	No
9/Male	Granular nodular	Right parietal	Yes	Yes	No
13/Female	Granular nodular	Right frontal	Yes	Yes	No
6/Male	Calcified	Right basifrontal	Yes	No	Yes

NCC: Neurocysticercosis

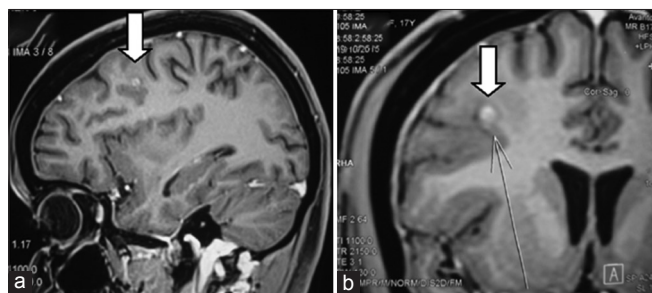


Figure 1: (a) CEMRI brain (sagittal) and (b) zoomed CEMRI brain (coronal) showing REL in the right frontal region

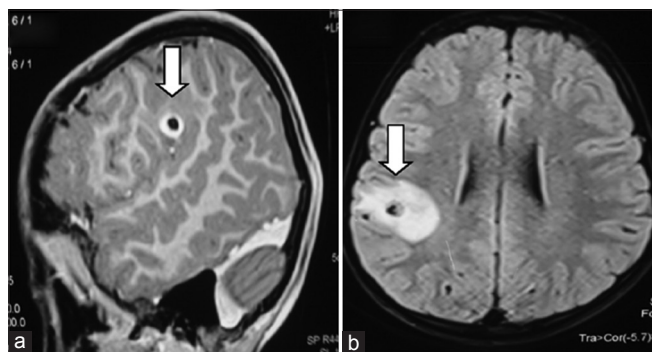


Figure 2: (a) CEMRI brain (sagittal) and (b) non-contrast FLAIR (Axial) showing REL in right parietal region with hypointense center and surrounding white matter hyperintensity suggestive of edema

(53.5%), 26.7% had multiple lesions, and 0.7% had midline shift. Significantly, the large number of patients was vegetarians (39%); only 17.6% were pork eaters while the remaining 82.4% never had pork in their meals [13].

Cysticercosis of the central nervous system (NCC) is caused by the larval stage (cysticerci) of the pork tapeworm *T. solium*. The two-host life cycle of this tapeworm comprises human beings as definitive hosts and swine as intermediate hosts. Pigs become infected when they ingest human feces containing *T. solium* eggs, which develop in the muscle and brain into cysticerci. When people eat undercooked pork containing viable cysticerci, they develop an intestinal tapeworm infection but not cysticercosis of the central nervous system. Human beings can also become intermediate hosts, however, by directly ingesting *T. solium* eggs shed in the feces of human carriers of the parasite. These eggs then develop into cysticerci which migrate mostly into muscle (causing cysticercosis) and into the central nervous system where the cysticerci can cause seizures and many other neurological symptoms (cysticercosis of the central nervous system). Both forms of human cysticercosis are, therefore, human-to-human infections acquired by the fecal–oral route in areas with poor hygiene and sanitation. Such a route of transmission is strongly supported by the concentration of cases of cysticercosis of the central nervous system in communities with human carriers of *Taenia*, where clustering of cases also supports the argument that carriers of *Taenia* are potent sources of contagion.

The results from the present study depict the prevalence rate of 10.3% of NCC among asymptomatic siblings of children with NCC. The significantly high prevalence rate of NCC in

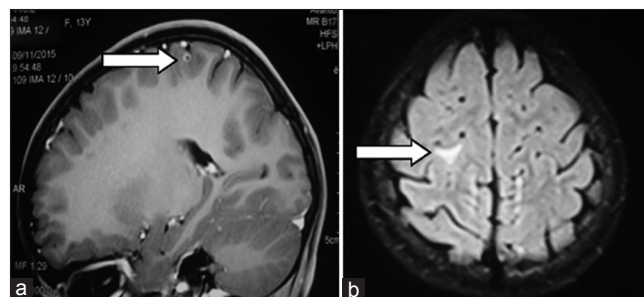


Figure 3: (a) CEMRI brain (sagittal) and (b) CEMRI brain (coronal) showing REL in the right frontal region

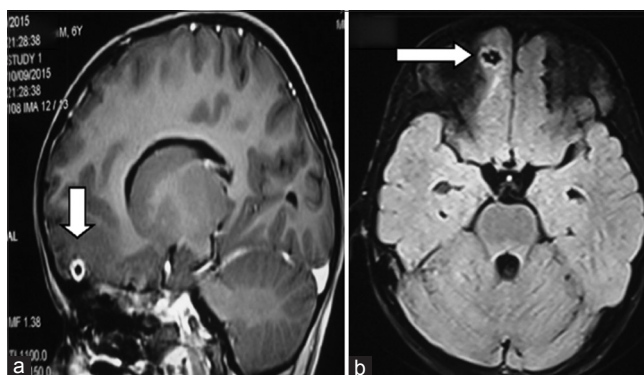


Figure 4: (a) CEMRI brain (sagittal) and (b) MRI brain FFE image showing REL in the right basifrontal region with blooming in the center, suggestive of calcification

the aforementioned asymptomatic siblings, in comparison to the reported prevalence rate for the Indian population, suggests possible clustering of cases of NCC within the family. Another peculiar finding in the present study was the absence of any symptoms in the enrolled siblings despite the presence of viable NCC lesions in majority (75%) of them, though even calcified lesions are no longer considered inactive as per recent reports [14]. Only one of the three children with viable NCC lesions developed symptoms in the form of unprovoked focal onset seizure during follow-up period of 1 year. A similar case of an asymptomatic 55-year-old Indian male with multiple subcutaneous and ocular cysticercosis along with multiple NCC in various stages of development has recently been reported [15]. A population-based study of residents over the age of 2 years in a highly endemic village in Peru (pop.454) using 14-question neurologic screening tool and evaluation of serum for antibodies against *T. solium* cysticercosis using enzyme-linked immunoelectrotransfer blot (LLGP-EITB) along with non-contrast computerized tomography (CT) of the head in residents over 18 years of age reported very high prevalence of seropositivity (36.9%) and brain calcifications consistent with NCC (18.8%) among asymptomatic residents [16]. These reports thus highlight that people with NCC can remain asymptomatic and only routine screening can help pick up such asymptomatic cases.

Cognitive impairment as an effect of NCC in school going children has been reported by Singhi *et al.* This was noticed to be seen mostly in children from lower socioeconomic status and in those with multiple lesion of NCC [17]. Similar observations have been made by Varghese *et al.* who reported an increase in interleukins to a significant level in vesicular stage of NCC and its association

with cognitive impairment. The number of lesions also correlated with cognitive impairment even though the location did not. The domains of cognitive deficits were seen in sustained attention, category fluency, verbal working memory, planning, set shifting, verbal learning, visual memory, and construction [18]. Prasad *et al.* found a significant difference in the intelligence quotient of NCC cases in domains of visual perception, immediate recall, analysis synthesis and reasoning, verbal ability, memory, and spatial ability. In the age group of 6–18 years, NCC cases had significantly more behavior problems than control without seizure, in domains of anxious depressed, withdrawn depressed, somatic problems, social problems, and rule-breaking behavior. Based on their observations, they suggested that NCC causes a decline in cognitive function and behaviors in older children, which should be recognized early for appropriate management and to avoid undue parental anxiety [19]. In a recent study by Del Brutto *et al.*, Atahualpa residents aged ≥ 40 years with calcified NCC were identified as case patients and paired 1:1 to age- and gender-matched controls (79 pairs). Cognitive performance was measured by the Montreal Cognitive Assessment (MoCA). A conditional logistic regression model revealed no differences in MoCA scores across case patients and controls, after adjusting for education, epilepsy, depression, and hippocampal atrophy. The single covariate remaining significant was hippocampal atrophy. When participants were stratified according to this covariate, linear models showed lower MoCA scores among case patients (but not controls) with hippocampal atrophy. In a fully adjusted linear regression model, age remained as the single covariate explaining cognitive impairment among NCC patients. This study demonstrates an association between hippocampal atrophy and poor cognitive performance among patients with calcified NCC, most likely attributable to the effect of age [20]. If larger studies replicate these observations, screening for NCC may then be proposed for children residing in *Taenia* endemic regions and presenting with cognitive impairment. However, mass screening of the population may not prove feasible as well as cost effective. The results from the present study suggest clustering of NCC cases in a family, and hence, family screening similar to screening for TB in family members of index pediatric case with TB may prove beneficial and cost effective.

Human cysticercosis and taeniasis are common in *Taenia* endemic regions. The major symptoms of human taeniasis reported by a study by De *et al.* include fidgeted anus (63.7–80.2%), proglottids moving to the anus or with the feces (82.9–92.1%), abdominal pain (59.7–62.1%), digestive disorder (45.2–50.0%), sleeplessness (35.2–39.5%), and hypotension (10.4–12.1%). Investigations for human taeniasis showed the following sensitivity rates: Positive *Taenia* eggs in stool (18.1–22.5%), increased eosinophils (76.1–81.1%), and enzyme-linked immunosorbent assay (ELISA) positives with *Taenia* antigen (72.2–76.7%). Human cysticercosis seroprevalence varied from 0.57 to 5.71% for circulating *T. solium* metacestode antigens and from 12.60 to 19.17% for *T. solium* antibody as per systematic review of seroepidemiological data from Asia [21]. Prevalence of human taeniasis in Asian continent has been reported to vary from 0.5–12% in Vietnam to 1.5% in

Laos [22,23]. An Indian study determined the seroprevalence of cysticercus antibodies in seizure-free, study subjects aged 2–60 years from urban and rural areas of Vellore district. Cysticercus antibodies, as determined by immunoblots, were noted in 15.9% of 1063 people and were significantly higher in the rural population (17.7%) compared with the urban population (6.0%). 24% of the rural population and 12% of the urban population ate pork [24]. In a similar study to detect the prevalence of taeniasis in North India using multistage stratified random sampling, 2500 subjects from urban (n=1250) and rural population (n=1250) of Lucknow, India, were enrolled. Serum ELISA was used to detect anticysticercus IgG and IgM antibodies. Microscopic examination of stool samples after processing by concentration method was done to observe taeniasis and other intestinal parasites. CT scan of seropositive cases presenting with seizures was done for confirmation of NCC. The overall, urban, and rural seroprevalences of *T. solium* cysticercosis were reported as 3.48%, 4.64%, and 2.32%, respectively. The risk factors significantly associated with the disease were pig rearing in both study populations, unsanitary waste disposal in urban, vegetarian diet, and open defecation in rural population. One case of intestinal taeniasis was observed. 26 of 30 cases undergoing CT scan were diagnosed as NCC [25]. The prevalence of taeniasis detected among family members of children with NCC was 1.7% in the present study. This value is much less than the reported prevalence rates of human taeniasis from India and hence does not suggest any clustering of taeniasis cases in family members of children with NCC. This suggests that the source of NCC infection detected in asymptomatic siblings is not *Taenia* carriers among family members. The findings from the present study regarding clustering of NCC cases in the family in the absence of clustering of taeniasis cases in the same family members suggest the role of common community food handlers, possibly being *Taenia* carriers, in the dissemination of NCC infection through contaminated raw food items such as fruits and vegetables. These findings, if replicated through larger studies, could prove highly beneficial in planning deworming policies targeting at community food handlers rather than mass community deworming, thereby proving more feasible and cost-effective health interventions. Moreover, the routine mass deworming as done as part of national programs needs to be introspected in terms of chances of precipitation of seizures in asymptomatic children with NCC as a result of cyst degeneration with cysticidal therapy in the absence of steroid cover. Hence, necessary supervision with staff and equipment readily available to tackle seizure occurrence may be advised in case of mass community/school deworming programs. Furthermore, targeted deworming of food handlers involved in mid-day meal programs implemented in government schools in India may also prove cost effective.

CONCLUSIONS

The study finding suggests that probably common food handlers from which raw fruits and vegetables are procured by the family or food handlers working in public eating joints are the source of infection leading to clustering of NCC cases among family members. Hence, targeted deworming of community food

handlers is proposed to be a more feasible and cost-effective public health intervention measure based on results from the present study. NCC is known to remain asymptomatic as was also seen in majority of the cases in the present study, and hence, caution is advised in conducting routine deworming of children as a part of national programs in terms of chances of precipitation of seizure(s) in children with asymptomatic viable NCC who receive cysticidal therapy in the absence of steroid cover. Such mass deworming sessions should be conducted with full preparation to deal with any such untoward event.

With a heavy heart, we inform the readers of the sad demise of the author. As a tribute, the corresponding author have written an obituary which is published at the end of this article.

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