

Neurocysticercosis : Clinical Manifestations and Assessments

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Abstract :

Background : In patients who have symptoms of epilepsy and other neurological deficits, one of the most common parasitic infections is neurocysticercosis (NCC) caused by *Cysticercus cellulosae*, the larval form of *Taenia solium*. In order to evaluate the characteristics of this illness which define the diagnosis, we assessed clinical manifestations, a positive ELISA for cysticercosis and neurological imaging in patients suspected of having NCC at a teaching hospital.

Methods : This retrospective cohort study assessed 44 patients, who had laboratory results and clinical manifestations compatible with a diagnosis of NCC, between November 1998 and November 2001. The criteria for diagnosing this illness modified from those of Del Brutto and colleagues' criteria. All patients were investigated with serum ELISA, 18 with CSF ELISA, if there was no contraindication. *T. solium* vesicular cyst soluble antigen was used for the detection of cysticercosis (*T. solium*) antibodies by solid-phase enzyme immunoassay. 35 patients were further investigated by a computerized tomography (CT) scan of central nervous system (CNS), if the results of other investigations were inconclusive. Using these criteria, we stratified all patients into three groups: possible NCC (19), probable NCC (10), and definite NCC (15). All "definite" patients were further examined with ELISA for *Angiostrongylus cantonensis* and Western blot for *Gnathostoma spinigerum* in order to look for cross-reactivity of the ELISA for cysticercosis.

Results : In this study, a prevalence of NCC (34.1%) in the group of patients in whom there was clinical suspicion of NCC makes us concerned that Thailand is still an endemic area for this disease. The three most common clinical presentations were seizures, neurological deficit, and signs of increased intracranial pressure. Serum ELISA showed a sensitivity of 33.3% and a specificity of 93.1%. CSF ELISA showed a sensitivity of 40.0% and a specificity of 100%. CT scan brain showed a high sensitivity (92.9%) with a modest specificity (52.4%). Cross-reaction with other parasitic proteins was found with *A. cantonensis* (6.7%), but not with *G. spinigerum*.

Conclusion : NCC is still endemic in Thailand. In the approach to this illness, we conclude that the diagnosis of NCC should be based on the patient's history and physical signs in combination with

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radiological and serological investigations. Moreover, in areas where *A. cantonensis* and *G. spinigerum* were also prevalent, case should be taken in the interpretation of a positive ELISA for cystercercosis because of cross-reactivity with antibodies to *A. cantonensis* which should be checked individually.

Key words : neurocysticercosis (NCC), ELISA, CT scan brain, *Taenia solium*, *Cysticercus cellulosae*, *Angiostrongylus cantonensis*, *Gnathostoma spinigerum*

เรื่องย่อ : โรคซิสติคเซอร์โคสิสที่ระบบประสาท: อาการแสดงทางคลินิกและการตรวจประเมินผล
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สารศิริราช 2545; 54: 394-402.

ในผู้ป่วยที่มีอาการแสดงของโรคลมชักและความบกพร่องทางระบบประสาทอื่นๆ พบว่า โรคซิสติคเซอร์โคสิสที่ระบบประสาท เป็นโรคติดเชื้อปรสิตที่พบบ่อยโรคหนึ่ง สาเหตุของโรคเกิดจากตัวอ่อน *Cysticercus cellulosae* ของพยาธิตืดหมู (*Taenia solium*) การประเมินลักษณะของโรคนี้เพื่อให้การวินิจฉัยโรค อาศัยลักษณะทางคลินิก การตรวจแอนติบอดีต่อพยาธิตืดหมูระยะตัวอ่อนให้ผลบวกด้วยวิธี ELISA และภาพถ่ายทางรังสีของระบบประสาท การศึกษาโดยอิมมูโนฟลูออเรสเซนซ์ในผู้ป่วยจำนวน 44 ราย ที่มีลักษณะทางคลินิกเข้าได้กับโรคซิสติคเซอร์โคสิสที่ระบบประสาท ระหว่างเดือน พฤศจิกายน 2541 ถึงเดือน พฤศจิกายน 2544 ผู้ป่วยทุกรายได้รับการตรวจเลือดด้วยวิธี ELISA ผู้ป่วยจำนวน 18 รายได้รับการตรวจน้ำไขสันหลังด้วยวิธี ELISA การตรวจด้วย ELISA ใช้แอนติเจนจาก *T. solium* vesicular cyst เพื่อตรวจหาแอนติบอดีต่อ cysticercus (*T. solium*) ผู้ป่วยจำนวน 35 ราย ที่ยังไม่ได้รับการวินิจฉัยโดยการตรวจอื่นๆ ได้รับการสืบค้นเพิ่มเติมด้วย คอมพิวเตอร์สแกน (CT scan) ที่ระบบประสาท เกณฑ์ในการวินิจฉัยโรคซิสติคเซอร์โคสิสที่ระบบประสาท ดัดแปลงมาจากเกณฑ์การวินิจฉัยโรคนี้ของ De' Brutto และคณะ จากเกณฑ์ดังกล่าวได้ แบ่งผู้ป่วยทั้งหมดออกเป็น 3 กลุ่ม ได้แก่ 1) ผู้ป่วยจำนวน 19 ราย อยู่ในเกณฑ์เป็นไปได้ (possible) ที่เป็นโรค 2) ผู้ป่วยจำนวน 10 ราย อยู่ในเกณฑ์อาจจะเป็น (probable) โรค 3) ผู้ป่วยจำนวน 15 ราย อยู่ในเกณฑ์เป็นโรคชัดเจน (definite) ผู้ป่วยทุกรายในกลุ่มที่ 3 ได้รับการตรวจเลือด และ/หรือ น้ำไขสันหลังเพิ่มเติมด้วยวิธี ELISA เพื่อตรวจหาแอนติบอดีต่อพยาธิ *Angiostrongylus cantonensis* และ วิธี Western blot เพื่อตรวจหาแอนติบอดีต่อพยาธิ *Gnathostoma spinigerum* เพื่อทดสอบการเกิดผลบวกข้ามกลุ่ม (cross-reactivity)

ในการศึกษานี้พบความชุกของโรคซิสติคเซอร์โคสิสที่ระบบประสาทในกลุ่มผู้ป่วยที่มีลักษณะอาการทางคลินิกที่น่าสงสัยว่าเป็นโรคนี้ ร้อยละ 34.1 ทำให้ตระหนักว่า โรคนี้ยังเป็นโรคประจำถิ่นในประเทศไทย ลักษณะทางคลินิกที่พบบ่อยที่สุดมี 3 ลักษณะ ได้แก่ อาการชัก ความบกพร่องทางระบบประสาท และอาการแสดงของภาวะความดันสูงในสมอง การตรวจแอนติบอดีต่อปรสิตในเลือดด้วยวิธี ELISA พบความไว ร้อยละ 33.3 และ

ความจำเพาะ ร้อยละ 93.1 การตรวจแอนติบอดีต่อปรสิตในน้ำไขสันหลังด้วยวิธี ELISA พบความไว ร้อยละ 40.0 และความจำเพาะ ร้อยละ 100 การตรวจ คอมพิวเตอร์ทอมोगรฟี พบความไว ร้อยละ 91.9 และความจำเพาะ ร้อยละ 51.4 การตรวจแอนติบอดีด้วยวิธี ELISA พบผลบวกข้ามกลุ่มเฉพาะพยาธิ *A. cantonensis* เท่านั้น (ร้อยละ 6.7) ไม่พบผลบวกข้ามกลุ่มของพยาธิ *G. spinigerum* เมื่อตรวจแอนติบอดีด้วยวิธี Western blot ผลสรุปการศึกษาพบว่า โรคซิสติคเฮอร์โคสิสที่ระบบประสาทยังคงเป็นโรคประจำถิ่นในประเทศไทย ในการวินิจฉัยโรคนี้ คณะผู้ศึกษาแนะนำว่า ควรอาศัยประวัติผู้ป่วย การตรวจร่างกาย ร่วมกับการตรวจทางห้องปฏิบัติการ ได้แก่ การสืบค้นทางระบบซีโรโลยี และการตรวจรังสีทางสมอง

INTRODUCTION

Taeniasis or pork tapeworm infection results from infestation with *Taenia solium*, the adult tapeworm, in the small intestine by consumption of raw or partially cooked pork that contains its larvae, cysticerci. Human are both the definitive and intermediate hosts for *T. solium*¹. In comparison, cysticercosis is a disease caused by the presence of *Cysticercus cellulosae* and *Cysticercus racemose*, the larval forms of *T. solium* in tissues. Infestation occurs after ingestion of *T. solium* eggs by fecal-oral transmission. In man either or both types of disease may be present^{1,2}. Cysticerci have a predilection for migrating to the central nervous system (CNS), eye and striated muscle because of the high glycogen or glucose content of these tissues³.

Neurocysticercosis (NCC) is an infection of the human CNS with the larval form of *T. solium*. Neurological involvement is the most common result^{2,4}. Clinical symptoms and signs of NCC are divided into parenchymal and extraparenchymal diseases. Parenchymal disease results from infection with cysticerci within the brain parenchyma. Extraparenchymal disease develops when cysticerci are found in the cerebrospinal fluid (CSF) in the ventricles, cisterns, and subarachnoid space or within the eyes or spinal cord. Its clinical manifestations are seizures, focal neurological deficits, increased intracranial pressure, vision change, and mental state change⁵⁻⁷. Although a diagnosis of NCC might be difficult to make, Del Brutto and colleagues have proposed criteria for the diagnosis⁸.

Serological methods and neurological imaging are both valuable in reaching a diagnosis. The use of an enzyme-linked immunosorbent assay

(ELISA) on an appropriate specimen is necessary. Serum ELISA and CSF ELISA measurements have been compared to determine which is the most appropriate specimen. This ELISA method can cross-react with some helminthic infections, in particular, with gnathostomiasis and angiostrongyliasis⁹. It is essential to perform an immunoblot for *Gnathostoma spinigerum* and *Angiostrongylus cantonensis* in order to confirm or refute the diagnosis of NCC and check cross-reactivity. A computerized tomography (CT) scan of the brain may be helpful, especially, if it shows a cyst containing a scolex or evidence of lesions suggestive of NCC without demonstrating a scolex or disappearance of the intracranial lesion after treatment with oral cysticercidal medication^{7,8}.

Unfortunately, we do not yet have a comprehensive picture of the prevalence and clinical features of NCC in Thailand^{4,9-21}, so that this study has evaluated not only the clinical manifestations and laboratory assessments of NCC but also the prevalence of NCC in patients in whom there was clinical suspicion of NCC at Siriraj Hospital. This data also report the cross-reactivity of the ELISA and Western blot for other helminthic diseases involving the CNS in similar patients.

MATERIALS AND METHODS

A retrospective cohort study was performed in 44 patients who were suspected of having NCC in the Department of Medicine at Siriraj Hospital from November 1998 to November 2001 and who also underwent investigations in the Department of Parasitology. The sample size required for this cohort was calculated by the SAM program²². The sample size required was 42 cases.

Forty-four patients were recruited in this cohort. Serum ELISA was performed in all patients. CSF ELISA was also performed in 18 patients, as there was no contraindication in these patients. In order to support the diagnosis, the CNS CT scan was done in 35 patients who had neurological deficit and/or symptoms and signs of increased intracranial pressure. The remaining patients had positive results for other diagnosis. Using Del Brutto and colleagues' criteria and adding a good clinical response after specific therapy (albendazole or praziquantel) to one of minor criteria, we divided patients into three groups: 19 with a possible diagnosis of NCC, 10 with a probable diagnosis of NCC, and 15 with a definite diagnosis of NCC. In the possible NCC, all patients had 1 major and 1 epidemiologic criteria. In the probable group, all patients had 1 major, 1 minor and 1 epidemiologic criteria. In the definite group, one patient had an absolute criterion with positive histological findings, and other 14 had 1 major, 2 minor and 1 epidemiologic criteria. ELISA investigation for *A. cantonensis* and Western blot analysis for *G. spinigerum* was performed in all definite patients. Almost all the possible and probable patients had a different final diagnosis: 1 had aseptic meningitis, 1 had cryptococcal meningitis, 1 had neurosyphilis, 2 had alcoholic dementia, 1 had lung carcinoma with a brain metastasis, 3 had cerebrovascular disorders, and 8 had eosinophilic meningitis.

T. solium vesicular cyst soluble antigen was utilized for the detection of cysticercosis (*T. solium*) antibodies by solid-phase enzyme immunoassay, using Cysticercosis Microplate ELISA (Chemicon International, USA). The cut off value was taken at 0.5 OD units and a test was considered to be positive when its value was greater than this. Antibody-detection ELISA was performed for *A. cantonensis*, which used its specific protein acting as the antigen^{20,21,23}. Western blot analysis, which can detect *G. spinigerum* at 24 kDa, if present was also performed²⁴.

Descriptive data analysis, crosstabulation, and chi-square tests, 1 sample K-S, Kruskal Wallis H tests were analysed. These data were calculated the SPSS program.

RESULTS

Data from 44 patients suspected of having NCC were collected and analysed. The demographic data are shown in Tables 1-3. Using modified Brutto and colleagues' criteria, we identified 15 definite cases of NCC. The prevalence of NCC among this cohort of patients was 34.1%.

The clinical manifestations of NCC are shown in Table 4. However, there is no discrimination in clinical manifestations not only between definite group and the rest, but also among three groups: definite, probable and possible groups. The symptoms and signs of increased intracranial pressure consisted of headache, and/or vomiting and/or papilledema.

In order to make a diagnosis, a CT scan brain was performed in 35 patients who also underwent other investigations. We found a compatible CT in 13 out of 14 (sensitivity 92.9%). However, it could rule out patients with suspected NCC who did not have it (false positive) in 10 out of 21 and showed a specificity of 52.4% (11 out of 21). Although a CT scan was performed in 14 out of 15 patients, who had a definite diagnosis of NCC, we found positive radiological findings in 13 out of 14 patients: multiple rings with or without enhancement (53.8%) were the most common radiological findings in this study. Others were calcified nodules (23.1%), an intracranial mass (23.1%) and hydrocephalus (7.7%) that were suggestive of NCC. The position of the lesions was frontal (53.8%), parietal (38.5%), temporal (23.1%), occipital (15.4%), midbrain (15.4%) and ventricle (7.7%).

ELISA for NCC was examined in both serum and CSF in order to determine the better specimen for the diagnosis of NCC. Serum values showed that 5 out of 15 patients clinically diagnosed with NCC were ELISA-positive; and 27 out of 29 were both free of disease and absolutely negative for this laboratory test. Serum ELISA showed a sensitivity in 33.3% and specificity 93.1%. CSF values showed that 2 out of 5 individuals clinically diagnosed with NCC were ELISA-positive. 13 patients who did not have NCC were also negative for the ELISA. CSF ELISA showed a sensitivity of 40.0% and a speci-

city of 100.0%.

Because of a confounding, cross-reaction with *A. cantonensis* and *G. spinigerum*, ELISA and Western blot analysis were performed specifically for

them respectively. We found our specimens cross-reacted with *A. cantonensis* in 1 out of 15 samples (6.7%), but did not cross-react with *G. spinigerum*.

Table 1. Sex distribution of possible, probable, and definite NCC.

Sex	Possible NCC	Probable NCC	Definite NCC	Total
Male	14 (73.7%)	3 (30.0%)	11 (91.7%)	29 (65.9%)
Female	5 (26.3%)	7 (70.0%)	1 (8.3%)	15 (34.1%)
Total	19 (100.0%)	10 (100.0%)	12 (100.0%)	44 (100.0%)

Table 2. Age distribution of possible, probable, and definite NCC.

Age range	Possible NCC	Probable NCC	Definite NCC	Total
≤ 20	3 (15.8%)	1 (10.0%)	2 (13.3%)	6 (13.6%)
21-40	12 (63.2%)	3 (30.0%)	4 (26.7%)	19 (43.2%)
41-60	3 (15.8%)	3 (30.0%)	5 (33.3%)	11 (25.0%)
> 60	1 (5.2%)	3 (30.0%)	4 (26.7%)	8 (18.2%)
Total	19 (100.0%)	10 (100.0%)	15 (100.0%)	44 (100.0%)

Table 3. Geographic data of possible, probable, and definite NCC.

Regions	Possible NCC	Probable NCC	Definite NCC	Total
Northern	1 (5.2%)	0 (0.0%)	2 (13.3%)	3 (6.8%)
Central	6 (31.7%)	6 (60.0%)	6 (40.0%)	18 (40.9%)
North-Eastern	10 (52.7%)	3 (30.0%)	4 (26.7%)	17 (38.6%)
Eastern	0 (0.0%)	0 (0.0%)	1 (6.7%)	1 (2.3%)
Western	1 (5.2%)	0 (0.0%)	2 (13.3%)	3 (6.8%)
Southern	1 (5.2%)	1 (10.0%)	0 (0.0%)	2 (4.6%)
Total	19 (100.0%)	10 (100.0%)	15 (100.0%)	44 (100.0%)

Table 4. Clinical manifestations of 15 definite NCC patients.

Clinical manifestations	No. of patients	Percent
Increased intracranial pressure	8	53.3
Neurological deficits	8	53.3
Seizures	8	53.3
Dizziness	3	20.0
Alteration of consciousness	1	6.7
Loss of cognitive	1	6.7

DISCUSSION

Cysticercosis is one of the most common parasitic infections that causes neurological abnormalities and has a high impact on the population worldwide not only in developing countries, but also in developed ones^{25,26}. White has described a high prevalence in Latin America, Africa, South and Southeast Asia, and Eastern Europe⁷. In this study, the prevalence of NCC was 34.1%. This prevalence is as high as that reported from endemic areas²⁷⁻³⁰. However, this study looked at individuals in whom the diagnosis was suspected, who presented to a teaching hospital. We did not have any cases from southern Thailand; this region may have a low rate of infestation as a result of the Islamic religion, fewer pigs being kept, and abstinence from eating pork. In a previous report, Gracia *et al* who studied factors associated with *T. solium* cysticercosis founded that living in rural area, having raised pigs, and being more than 20 years of age with a history of seizure were significant factors associated with NCC²⁸. Actually, economic, cultural and religious factors strongly affect the prevalence of cysticercosis in any particular geographical area³.

NCC can present with a variety of symptoms and signs. In this study, three common clinical manifestations were seizures, neurological deficit, and signs of increased intracranial pressure (53.3%). This resembles other reports from India and Thailand. Kuruvilla *et al* discovered that the most common clinical presentation was seizure (100%) followed by headache/vomiting (64%), papilledema (27%) and neurological deficits (18%)³¹, and Vejajiva also found that *Cysticercus cellulosae* commonly results

in epilepsy, and sometimes increased intracranial pressure. However, spinal cord and cauda equina involvement occurs much less frequently⁴. Nevertheless, Sotelo *et al* who studied in 753 cases of NCC in Mexico found other clinical manifestations are common: arachnoiditis (48%) and hydrocephalus due to meningeal inflammation (25.7%) were the most common form³². Perhaps, because of the different states of cysticercosis in the CNS, patients demonstrate a variety of symptoms and signs so that clinical manifestations differ according to region³. Thus, Scharf has concluded that the clinical manifestations of NCC are related to several factors: size, number, and location of the cysts and the host-cyst inflammatory response²⁵. In this retrospective study, seizures (53.3%) was also the most frequent clinical manifestation and focal seizures with secondary generalization were the most common (75%) of all. As in a previous report in which McCormick *et al* suggested that focal or generalized seizures are the most common symptoms occurring in up to 92%³³.

A CT brain scan is widely accepted as the first line imaging required in patients suspected of having NCC¹⁻³. In this study, we found various characteristics that might suggest NCC: the sensitivity of imaging was high but the specificity was moderate so that both false-positives and false-negatives occurred at a high rate. The results of this procedure depend on the stage of the lesion and the host inflammatory response^{3,4}.

In this study, the sensitivity and specificity of serum ELISA was 33.3% and 93.1% respectively for diagnosing NCC so that it is hard to use serum

ELISA alone for the diagnosis of this disease unless there is other useful evidence. Contrary to this, the sensitivity of ELISA varied from 50% to 90%^{9,10,35,36}. We showed no discrimination between two different specimens (serum and CSF) in that ELISA in CSF was as sensitive as serum in diagnosing NCC. As in a previous study, White found serum and CSF had similar sensitivities between 60% and 80%³⁷. Although there is controversy concerning which specimen to use, Del Brutto *et al* have recommended one criterion for diagnosing NCC as positive serum anticysticercal antibodies demonstrated by immunoblot, or positive CSF anticysticercal antibodies demonstrated by immunoblot or ELISA⁸. Interestingly, it has been suggested that specimens should be further investigated with enzyme-linked electroimmunotransfer blot (EITB) for NCC. Tsang *et al* suggested that EITB has a sensitivity of 100% and specificity of nearly to 100% in the confirmation of the diagnosis³⁸. However, Ito *et al* have reported that not only immunoblots but also ELISA show very similar sensitivities and specificities for the differentiation of NCC from other disease³⁹.

In Thailand, there are three parasites and a protozoan that commonly cause neurological disease in man. These are *T. solium* (cysticercosis), *G. spinigerum*, *A. cantonensis*, and *Toxoplasma gondii*⁴⁰. We were concerned that ELISA results could show a false positive for other parasitic infections, particularly *A. cantonensis* and *G. spinigerum*. In this study, either an ELISA or Western blot analysis was performed in order to prevent this. Similar to others, we still found cross-reactivity of helminthic protein with *A. cantonensis*

(6.7%), but not with *G. spinigerum*^{9,10}. However, in order to eradicate false positive and false negative results, Ito *et al* have suggested methods of specific antigen purification, and isoelectric focusing, in order to produce cystic fluid with purified glycoprotein that shows almost no cross-sensitivity and which is useful for immunoblots and ELISA^{39,41}.

CONCLUSION

NCC is one of the parasitic infestations, which involves the CNS and is endemic in Thailand. Seizures, local neurological deficits, and signs of increased intracranial pressure are common and may provoke clinical suspicion of the disease. Nevertheless, it is not possible to make the diagnosis with inadequate evidence. In order to diagnose NCC, it is essential to integrate clinical manifestations, immunodiagnosis, neurological imaging, the response to therapy, and pathological evidence in order to reach a definite diagnosis. Because ELISA has a low sensitivity but high specificity to NCC, we recommend that the combination of all evidence is still essential. In this study, we found CSF ELISA values were not different from serum ELISA values. However, this conclusion needs further investigation by a prospective study. The cross-reactivity of parasites, that causes CNS infections: *A. cantonensis*, *G. spinigerum* and *C. cellulosae*, should be clarified using appropriate laboratory techniques and the antigen detection of these parasites should be explored further in order to achieve easier and more reliable, accurate diagnosis of NCC.

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