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Comparative Evaluation of Brain CT and ELISA in the Diagnosis of Neurocysticercosis

Kee Hyun Chang[1]
Woo Sun Kim[1]
Seung Yull Cho[2]
Man Chung Han[1]
Chu-Wan Kim[1]

This study compares the results of cysticercus-specific IgG antibody levels, as measured by enzyme-linked immunosorbent assay (ELISA), with brain CT findings in suspected neurocysticercosis and to assess the clinical significance of ELISA. One hundred twenty-three neurologic patients were examined by both brain CT and ELISA. Sensitivity and specificity of ELISA in confirmed cases were 94% and 91%, respectively. Patients with multiple cysts without enhancement on CT, which were thought to represent viable cysticerci, were positive by ELISA. Those with cysts with enhancement or poorly defined low densities or enhancing nodules, which represented cysticerci on degeneration, were also positive by ELISA. Those with multiple spotty calcifications, which represent cysticerci in the inactive stage, were negative by ELISA. Those with mixed CT findings of the above, which represent the various stages of infection in a patient, were positive by ELISA. Those with only enhancing nodules with surrounding edema, which were thought to be other inflammatory granulomas, were negative by ELISA. If patients with only hydrocephalus on CT are positive by ELISA, they can be confidently diagnosed as having ventricular cysticercosis.

The results indicate that ELISA is useful as a complementary diagnostic tool, especially in patients with equivocal CT findings of neurocysticercosis. Provision of etiologic information on a biologic basis was the advantage of this serologic test.

CT remains the primary diagnostic tool for neurocysticercosis. CT demonstrates the exact location and extent of the lesions, allowing appropriate decisions to be made regarding diagnosis and treatment in most patients [1–9]. The MR appearance of cysticercosis has been reported [10], but the specific role of MR in this disease has not yet been defined. In some cases, however, diagnosis by CT is difficult, especially when CT findings are atypical or equivocal. In addition, in the radiologic diagnosis of ventricular cysticercosis, conventional or CT ventriculography, an invasive procedure, is needed frequently to demonstrate the specific location of the cyst. It is hoped MR will replace ventriculography in these patients.

Before the development of CT, another approach to the diagnosis of neurocysticercosis, serologic testing, was used. Recently, enzyme-linked immunosorbent assay (ELISA) has been applied to measure cysticercus-specific IgG antibody in both serum and CSF. ELISA is known to have a high sensitivity and specificity in the diagnosis of neurocysticercosis. It has been used increasingly as a diagnostic procedure for suspected neurocysticercosis [11–18]. ELISA could be a complementary test, especially in the evaluation of patients with atypical CT findings of neurocysticercosis, such as enhancing nodules or only obstructive hydrocephalus without multiple cysts. Also, it may reduce the need for invasive ventriculography.

These two diagnostic methods, CT and ELISA, have different advantages and drawbacks. We believed a comparison of the CT findings and the results of ELISA in a variety of neurocysticercosis patients would help clarify their contributions. The purposes of this study were to evaluate the diagnostic ability of ELISA and its correlation with CT findings, and to determine the clinical significance of ELISA in diagnosing neurocysticercosis.

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[1] Department of Radiology, College of Medicine, Seoul National University, Seoul 110, Korea. Address reprint requests to K. H. Chang, Department of Diagnostic Radiology, Seoul National University Hospital, 28 Yeongun-Dong, Chongro-Ku, Seoul 110, Korea.

[2] Department of Parasitology, College of Medicine, Chung-Ang University, Seoul, Korea.

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Materials and Methods

Of the neurologic patients admitted to Seoul National University Hospital from January 1984 to October 1985, 123 consecutive patients with suspected neurocysticercosis were examined by both CT and ELISA. The patients were 13–69 years old. Seventy-two patients were male and 51 were female. Fourteen patients underwent brain surgery, of which 11 cases were confirmed pathologically as cysticercosis and three were confirmed as other diseases. CT scans of the brains were obtained in the routine axial projection, both before and after administration of contrast material.

ELISA was done to measure the levels of cysticercus-specific IgG antibody in serum (1:100 diluted) and undiluted CSF from the patients (Department of Parasitology, Chung-Ang University). Cystic fluid of *Cysticercus cellulosae* was used as an antigen [17]. The principles, techniques, and criteria for positive reaction of ELISA have been described in detail elsewhere [16]. In 121 cases, ELISA was done for both serum and CSF. In two cases, only serum was examined by ELISA. Positive results of ELISA in either serum or CSF or both were regarded as positive.

Each CT scan was reviewed retrospectively without knowledge of the results of ELISA or surgery. On the basis of the CT findings, patients were grouped into CT-positive, CT-suggestive, or CT-negative for neurocysticercosis by the following criteria. The CT-positive group consisted of 29 patients with multiple, round cystic lesions of low density, each containing a tiny eccentric nodule, representing the scolex of the worm with or without cystic wall enhancement or nodular enhancement (Fig. 1). Six of 11 surgically proved cases of cysticercosis were included in this group. The CT-suggestive group consisted of 40 patients who showed equivocal CT findings such as hydrocephalus only (Fig. 2), a single cystic lesion (Fig. 3), multiple spotty calcifications (Fig. 4), or enhancing nodules without cystic lesions (Figs. 5 and 6). Five cases with hydrocephalus only on CT were surgically confirmed as ventricular cysticercosis. The CT-negative group comprised 54 patients with either normal CT findings or definite findings of other diseases. Three cases confirmed surgically as other diseases were included here.

All patients in the CT-positive group, in addition to the surgically proved cases, were considered as definite cases of neurocysticercosis and were included in statistical calculations of the accuracy of ELISA; the above-mentioned CT findings for the CT-positive group are virtually pathognomonic of neurocysticercosis, particularly in an endemic area such as Korea. Only typical cases were included in the CT-positive group.

Results

The relationships between ELISA results and CT findings are shown in Table 1. The positive rates by ELISA were 93.1%, 42.5%, and 9.3% in the CT-positive, CT-suggestive, and CT-negative groups, respectively.

The diagnostic accuracy of ELISA in this study is summarized in Table 2. Among the 34 patients with neurocysticercosis, consisting of five surgically proved cases in the CT-suggestive group and 29 cases in the CT-positive group, only two patients were negative by ELISA in both serum and CSF (sensitivity of 94%). One of the two false-negative cases showed multiple cystic lesions in the brain parenchyma on CT, and these were pathologically proved to be cysticerci. The other case was not surgically proved, but showed multiple cystic lesions and spotty calcifications on CT.

The 54 cases of nonneurocysticercosis comprised 50 patients with normal CT and four patients with other diseases (one case each of cystic meningioma, metastasis of lung cancer, pituitary tumor, and subarachnoid hemorrhage with hydrocephalus). Among them, five patients were false-positive by ELISA in serum and/or CSF (specificity of 91%). Two of the five cases, confirmed as cystic meningioma and pituitary adenoma, were falsely positive by ELISA in both serum and

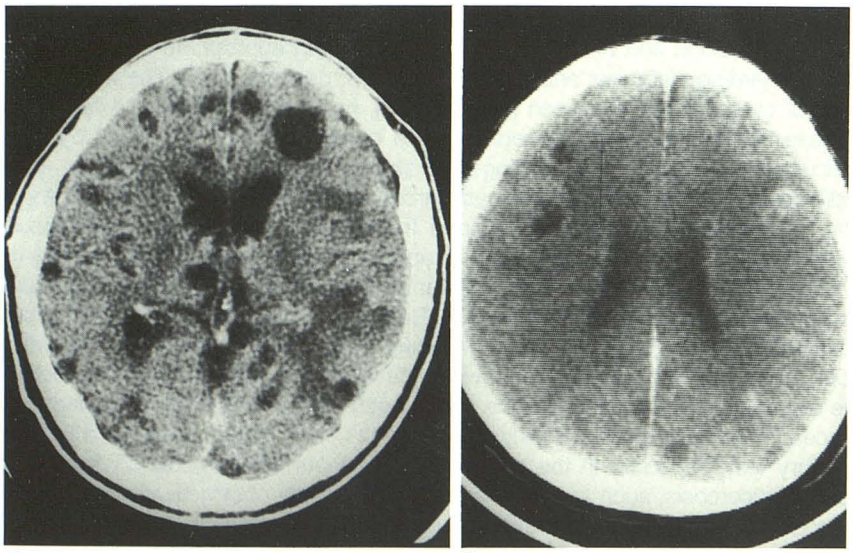

Fig. 1.—Typical cases of cysticercosis in CT-positive group. ELISA was positive in both cases.
***A*, Multiple cysticerci without reactive change in brain parenchyma, suggesting viable cysticerci.**
***B*, Multiple cysticerci, some with reactive parenchymal change, indicating cysticerci in various stages.**

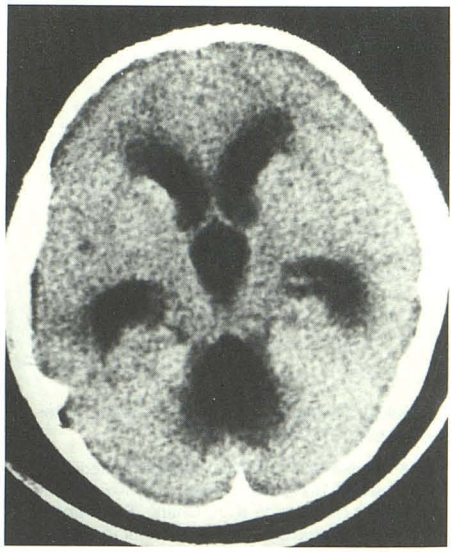

Fig. 2.—CT-suggestive but ELISA-positive case with hydrocephalus only on CT. This case was surgically proved to have cysticercosis in fourth ventricle.

Fig. 3.—CT-suggestive but ELISA-positive case with solitary cyst in left temporoparietal area. Solitary cysticercosis was proved at surgery.

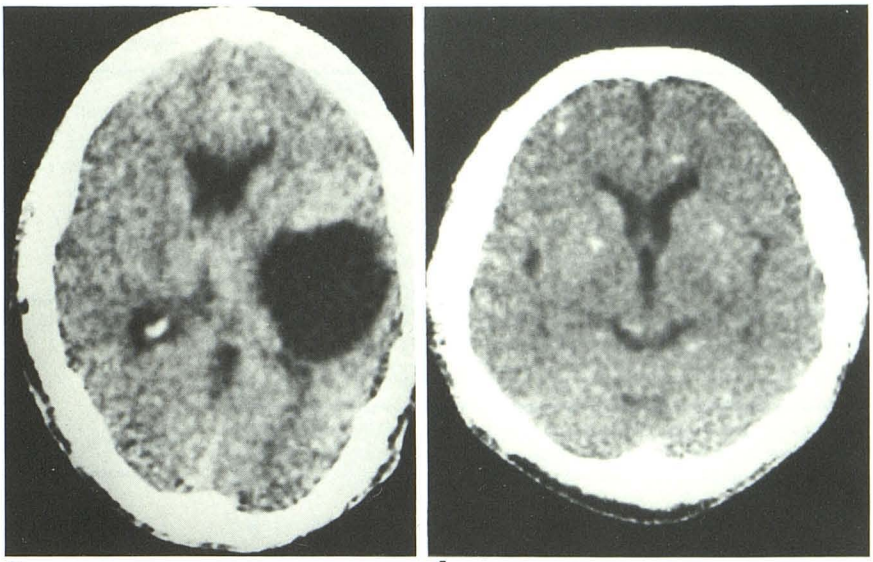

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Fig. 4.—CT-suggestive but ELISA-negative case with multiple spotty calcifications, thought to result from negative seroconversion of inactive cysticercosis.

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Fig. 5.—CT-suggestive but ELISA-positive case with multiple enhancing nodules, strongly suggesting degenerating cysticerci.

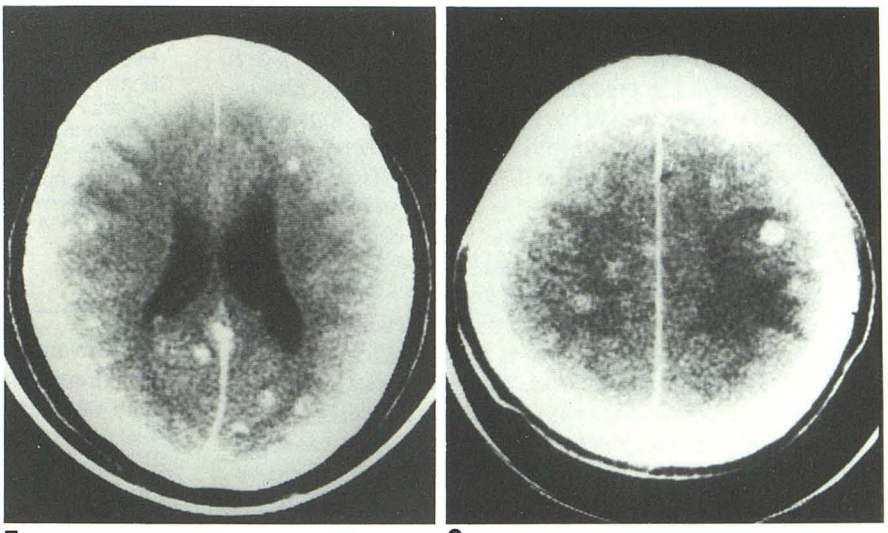

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Fig. 6.—CT-suggestive but ELISA-negative case with multiple enhancing nodules associated with surrounding edema. Inflammatory granulomas from causes other than cysticercosis or degenerating cysticerci with false-negative ELISA. Presumed multiple tuberculomas in patient with confirmed pulmonary tuberculosis of miliary type.

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TABLE 1: Correlation of ELISA Results with CT Findings

Results of ELISA	No. of Cases			
	Total	CT-Positive	CT-Suggestive	CT-Negative
Positive	49	27 (5)[a]	17 (5)[a]	5 (2)[b]
Negative	74	2 (1)[a]	23	49 (1)[b]
Total	123	29	40	54

Note.—ELISA = enzyme-linked immunosorbent assay.

[a] Numbers in parentheses indicate surgically confirmed neurocysticercosis.

[b] Numbers in parentheses reflect other surgically confirmed neurologic diseases (one cystic meningioma, one cystic pituitary adenoma, and one metastasis).

CSF. Three patients were false-positive with only serum but not with CSF. Two of the three cases had a normal brain CT scan, of which one had biopsy-proved subcutaneous cysticercosis. The remaining one case with false-positive ELISA only in serum showed multiple ring-enhancing nodules with surrounding edema, which turned out to be metastatic tumors.

The remaining 35 patients without surgical proof in the CT-suggestive group were classified as a nonclarified, which was not considered in calculations of diagnostic accuracy.

Of 11 surgically proved neurocysticercosis cases, all five patients with only hydrocephalus on plain CT revealed a

TABLE 2: Diagnostic Sensitivity and Specificity of ELISA

ELISA	No. of Cases (No. Confirmed)[a]		
	Neurocysticercosis	Nonneurocysticercosis	Not Clarified
Positive:			
Serum and CSF	28	2	–
Serum only	1	3	–
CSF only	3	0	–
Subtotal	32 (10)	5 (2)	12
Negative	2 (1)	49 (1)	23
Total	34[b] (11)	54[c] (3)	35[d]

Note.—ELISA = enzyme-linked immunosorbent assay; CSF = cerebrospinal fluid. Overall sensitivity of ELISA = 32/34 = 94% (85% for serum and 91% for CSF); overall specificity of ELISA = 49/54 = 91% (91% for serum and 96% for CSF).

[a] Confirmation was by surgery and histology.

[b] Comprises 29 CT-positive cases and five surgically proved cases in CT-suggestive group.

[c] Comprises 50 cases with normal brain CT and four with other disease in CT-negative group.

[d] Comprises 35 CT-suggestive group patients without surgical proof.

TABLE 3: Location of Lesions in Patients with Neurocysticercosis

Location of Lesion	No. of Cases	
	Positive ELISA	Negative ELISA
Parenchyma only	15	2
Cistern only	1	0
Ventricle only	5	0
Combination	11	0
Total	32	2

Note.—ELISA = enzyme-linked immunosorbent assay.

TABLE 4: CT Findings in Patients with Neurocysticercosis

CT Findings	No. of Cases	
	Positive ELISA (n = 32)	Negative ELISA (n = 2)
Multiple cysts:		
Without enhancement	16	1
With enhancement	4	0
Some with and some without enhancement	7	1
Multiple cysts with:		
Spotty calcifications	13	1
Hydrocephalus	14	0
Enhancing nodules	4	1
Enhancing nodules with surrounding edema	1	0
No other findings	6	1
Only hydrocephalus	5	0

Note.—ELISA = enzyme-linked immunosorbent assay.

positive reaction by ELISA in both serum and CSF, which prompted additional preoperative evaluation with conventional or CT ventriculography to determine the appropriate surgical approach. This means that ELISA could play a crucial role not only in diagnosing a patient with CT findings of hydrocephalus only, but also in making a decision as to whether ventriculography or cisternography is necessary.

As shown in Table 3, positive reactivity by ELISA appears to be somewhat lower in patients with the parenchymal vs the cisternal or ventricular form. Two patients who were false-negative by ELISA showed lesions in the brain parenchyma on CT. The level of IgG antibody in the CSF was somewhat higher in the cisternal and ventricular forms than in the parenchymal form, but it was not statistically significant. Nonetheless, our neurocysticercosis cases with cisternal, ventricular, or combined locations were all positive by ELISA for CSF.

The CT findings in 34 neurocysticercosis cases are summarized in Table 4. In patients with positive ELISA, contrast enhancement around the cysts, spotty calcification, hydrocephalus, and enhancing nodules with or without surrounding edema were associated with multiple cysts (Fig. 1B). This suggested that these associated findings did not affect the results of ELISA if multiple cysts of low density were present on CT. All five patients with only hydrocephalus on CT were surgically confirmed as having intraventricular cysticercosis. Two patients with false-negative ELISA also revealed multiple cysts similar to the positive cases.

The 40 cases in the CT-suggestive group (including five surgically proved cases) were divided into 17 ELISA-positive and 23 ELISA-negative (Table 5). Among the 17 ELISA-positive cases, a low-density area (not round) without enhancement was found in five, a low-density area with spotty calcifications was found in three, and only hydrocephalus was observed in seven. Of the 23 ELISA-negative cases, those findings were found in one, zero, and two patients, respectively. Enhancing nodules with surrounding edema, only spotty calcifications, or a combination of the two findings were found in 13 ELISA-negative cases but in no ELISA-positive cases. The number of the cysts did not affect the ELISA results (Table 5).

The relationship between CT findings and degree of ELISA titer in the CSF is shown in Table 6. The level of CSF ELISA was arbitrarily divided into two groups: mild to moderately elevated, in which absorbance ranged from 0.18 to 0.25, and markedly elevated, in which absorbance was higher than 0.26. The CT-positive group tended to have a higher level of antibody when compared with the CT-suggestive group. Six of seven patients with only hydrocephalus on CT showed a markedly elevated level of antibody in the CSF. No other relationship was found between the antibody level and the CT findings.

Discussion

The CT findings of neurocysticercosis are variable and depend fundamentally on three factors: number, location, and stage in evolution of the infection. Viable cysticerci in the brain parenchyma are known to be inert and appear as round

TABLE 5: Correlation of CT with ELISA in the CT-Suggestive Group

CT Findings	No. of Cases	
	Positive ELISA	Negative ELISA
Low-density area (not round):		
Without enhancement	2 S	0 S
	3 M	1 M
With enhancement	0 S	2 S
	1 M	1 M
Combined with spotty calcification	3	0
Combined with hydrocephalus	1	1
Combined with enhancing nodule	0	1
Combined with meningeal enhancement	1	0
Combined with no other findings	1	2
Subtotal	6[a]	4[a]
Only hydrocephalus	7[b]	2
Only enhancing nodule:		
Without surrounding edema	1 S	2 S
	1 M	1 M
With surrounding edema	0 S	5 S
	0 M	1 M
Subtotal	2	9
Only spotty calcification	0 M	3 S
	0 M	2 M
Spotty calcification and enhancing nodule	0	2
Meningeal enhancement:		
Combined with hydrocephalus	1	1
Combined with spotty calcification	1	0
Subtotal	2[c]	1
Total	17	23

Note.—ELISA = enzyme-linked immunosorbent assay; S = solitary; M = multiple.

[a] The two different categories of low-density areas (enhancement and other features) each contain the same group of six (positive) or four (negative) patients.

[b] Of seven cases, five were surgically proved to be ventricular cysticercosis.

[c] Meningeal enhancement was seen in three cases in the positive ELISA group. One case is included under low-density area.

TABLE 6: Relationship Between CT and Degree of ELISA Level in CSF

ELISA Level	No. of Patients (No. Showing Only Hydrocephalus)	
	CT-Positive Group	CT-Suggestive Group
Mild to moderately elevated	6	8 (1)
Markedly elevated	21	9 (6)

Note.—ELISA = enzyme-linked immunosorbent assay.

cysts of low density without enhancement or edema on CT [1, 8, 9].

After a variable period (probably more than 5 years), the cysticerci begin to degenerate [1, 8]. This process evokes a granulomatous response with edema and cellular infiltration, producing an acute encephalitis stage [1, 8, 9]. On CT, this phase shows multiple diffuse (85%) or localized (15%) enhancing nodular or ringlike lesions associated with brain edema [9]. This process lasts 2–6 months; on subsequent CT scans, cerebral edema and ventricular dilatation subside. Finally, the enhancing lesions disappear, and the granulomatous lesions are replaced by gliosis to become calcified nodules (Figs. 4 and 5). CT findings in the acute encephalitic phase are sometimes difficult to differentiate from multiple tuberculomas, small abscesses, metastases, or mycoses [9]. In our series, seven patients had enhancing granulomas with surrounding edema on CT (Fig. 6), but had no history of raw-pork ingestion or skin nodules and were negative by ELISA. Therefore, they were thought to represent inflammatory granulomas of other causes.

So far, CT is the most useful imaging method in screening for neurocysticercosis. It is not possible, however, to make a definite diagnosis in every case. In cases with nonspecific findings on CT, such as hydrocephalus only, a single cystic lesion, multiple spotty calcifications, or single or multiple enhancing granulomatous lesions, CT affords only a presumptive diagnosis. Therefore, to achieve a higher level of certainty, some cases require adjuvant methods of diagnosis. Perhaps MR will assist in the differential diagnosis.

Since the early 1950s, various serologic tests (such as the indirect hemagglutination test) have been applied to the diagnosis of cysticercosis. But their diagnostic accuracy has been reported to be variable; the sensitivity was 10–92% and nonspecific reactions in the range of 4–25% were observed [1, 7, 11–16]. Since 1978, when ELISA was applied to cysticercosis by Arambulo et al. [11], it has been proved to show a higher sensitivity and specificity than other serologic tests. Recently, ELISA with serum and CSF was reported to show a 90.1% sensitivity and 88.5% specificity [16]. Even in ELISA, however, problems exist. Some cysticercosis infections do not stimulate a detectable level of antibody [11–16]. Measuring both serum and CSF is helpful to improve the diagnostic reliability. A few patients have antibodies either only in serum or in CSF [14, 16]. CSF is known to be more sensitive and specific [16]. In our series, sensitivity and specificity of CSF ELISA were 91% and 96%, respectively, while those of the serum test were 85% and 91% (Table 2).

By location of the diseases in the central nervous system, it has been suggested that the immunologic reaction is greater in meningitis and ventricular cysts than in simple parenchymal lesions. Miller et al. [15] observed that ELISA showed nearly a 100% sensitivity for ventricular cysts and meningitis, while sensitivity was 86% for parenchymal cysts. In our patients, the two cases that were false-negative by ELISA were parenchymal. Our results, together with previous reports, suggest that the possibility of false-negative results by ELISA may be higher in patients with only parenchymal disease.

Immunologic responses take time to develop, and a negative conversion may occur in the early stage of infection, as well as in the late, inactive stage [15, 16, 18]. In our CT-suggestive group, five patients who had only spotty calcifications on CT were all negative by ELISA. Similarly, two cases of spotty calcification with enhancing nodules showed

negative results by ELISA. Considering the natural course of the cysticercus from cysts to calcifications, some or all of these cases could be negative seroconverters (Fig. 4), but the possibility of other causes of calcifications cannot be ruled out.

In conclusion, even though there were false-positive and false-negative results in our cases, ELISA was a very sensitive method in the diagnosis of neurocysticercosis from viable worms. Results of ELISA correlated reasonably well with CT findings, taking into consideration the stage of infection. As a result, patients who need praziquantel treatment can be selected on the basis of CT and ELISA. ELISA was especially helpful in the evaluation of patients with equivocal CT findings. For example, in patients with only hydrocephalus on CT, since a negative ELISA result makes cysticercosis an unlikely diagnosis, invasive ventriculography can be reserved for only ELISA-positive patients.

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