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# Neurocysticercosis: experience with diagnosis by ELISA serology and computerised tomography in Zimbabwe

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## SUMMARY

Over a three-year period, 646 sera from 630 patients with signs and symptoms compatible with neurocysticercosis were investigated for antibodies to cysticercal antigens using an ELISA test. Overall, 12 pc specimens were positive. The sensitivity of the ELISA, when compared with a limited number of computerised tomography investigations, was over 70 pc. False negative serology was associated with HIV infection in some patients.

The positive predictive value was 87 pc and the negative predictive value was 85 pc when patients with active infection, potentially amenable to chemotherapy, were considered. The specificity, determined from serological tests of patients with a variety of trematode, cestode and other infections, was over 90 pc. Three of 11 patients with intestinal taeniasis, and each of two patients with hydatid disease were seropositive.

The results suggest the value of ELISA serology as a more cost-effective diagnostic method for all patients with suspected cysticercosis.

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## INTRODUCTION

Neurocysticercosis (NCC) is the most important parasitic disease of the central nervous system worldwide and is a significant public health problem in many developing countries.<sup>1,2</sup> It has been reported in up to 3.6 pc of autopsies in Mexico City and was found to account for about 10 pc of neurology admissions there.<sup>3</sup> In a study of mine workers with newly diagnosed epilepsy in South Africa, computed tomography (CT) showed 37 pc to have calcified or inactive lesions and 14 pc to have viable cysts.<sup>4</sup> NCC was considered to be the cause in 30 pc of patients presenting with "idiopathic epilepsy" in Natal.<sup>5</sup> In Zimbabwe, calcified cysticerci are not uncommon incidental findings on chest or limb X-rays and NCC is an occasional diagnosis at surgery for intracranial or spinal lesions. A study in Bulawayo found calcified cysticerci in 11 pc of patients presenting with seizures in whom thigh X-rays were taken.<sup>6</sup>

The early diagnosis of NCC has become important because of the success of chemotherapy, using albendazole or praziquantel, for treatment of patients with viable cysticerci. Clinical diagnosis is highly unreliable<sup>7</sup> and X-ray examinations will reveal only calcified cysts which are not amenable to treatment. While CT is widely regarded as the best method for detecting cysticerci, it is unlikely to be widely available in developing countries because of its cost.

There is thus a need for an inexpensive and reliable diagnostic test suitable for use in developing countries. Recent attention has focused on immunological diagnosis<sup>9, 10</sup> and in Zimbabwe an ELISA test was developed for detecting serum antibodies to antigens extracted from the fluid of live cysticerci.<sup>11</sup> Limited experience demonstrated a good correlation between positive serology and active cysticercosis, though responses in patients with inactive, calcified lesions were more variable.<sup>11</sup> We here report on our experience with diagnosing NCC over a three-year period during which the ELISA test was made available as a routine clinical service, and in which funds were available for a limited number of CT scans.

## MATERIALS AND METHODS

**Patients:** Patients were recruited from several sources. Staff at the two Harare teaching hospitals were encouraged to send clotted blood specimens from all in- or out-patients presenting with seizures, suspected mass lesions or other neurological syndromes compatible with NCC. We attempted to contact all patients with positive serology to obtain a CT scan. In addition, a number of patients who had NCC diagnosed on CT scan in the course of their clinical investigation or as part of a study on intracranial mass lesions and HIV-related neurological disorders, were included in this study, and clotted blood was obtained from them. Blood and CT scans were also requested from a few patients in whom a diagnosis of cysticercosis was made by biopsy.

In order to obtain information on NCC in other groups of patients, we reviewed 68 CT scans from patients with a history of acute stroke, and we obtained clotted blood from patients with a variety of cestode, trematode and other infectious diseases common in Zimbabwe, as well as from 61 patients enrolled in a community study of seizure treatment.

**CT Scans:** The CT scans were performed in most cases both with and without contrast enhancement and the scans were interpreted by a neurologist experienced in both CT and NCC. Examples of the scans obtained and their interpretation are shown in Figures I-III.

**ELISA serology:** Sera were separated from the clotted blood specimens and were stored frozen at  $-20^{\circ}\text{C}$  before testing. The NCC ELISA was carried out using a method modified from that described previously.<sup>11</sup> Briefly, micro-titre ELISA plates were coated overnight at  $4^{\circ}\text{C}$  with antigen (prepared from fluid expressed from live cysticerci and stored at  $-70^{\circ}\text{C}$ ) containing  $10\ \mu\text{g}$  protein in  $100\ \mu\text{l}$  carbonate buffer (pH 9). After washing three times with phosphate buffered saline containing 0.05 pc Tween 20 (PBST, pH 7.3),  $50\ \mu\text{l}$  serum (diluted 1/200 in PBST) was added to duplicate wells and incubated for 45 minutes at  $37^{\circ}\text{C}$ . Appropriate positive and negative sera were included with each run. After washing as above,  $50\ \mu\text{l}$  peroxidase-labelled anti-human IgG (Cooper Biomedical, USA, diluted 1/3000 with PBST) was added to the wells and plates

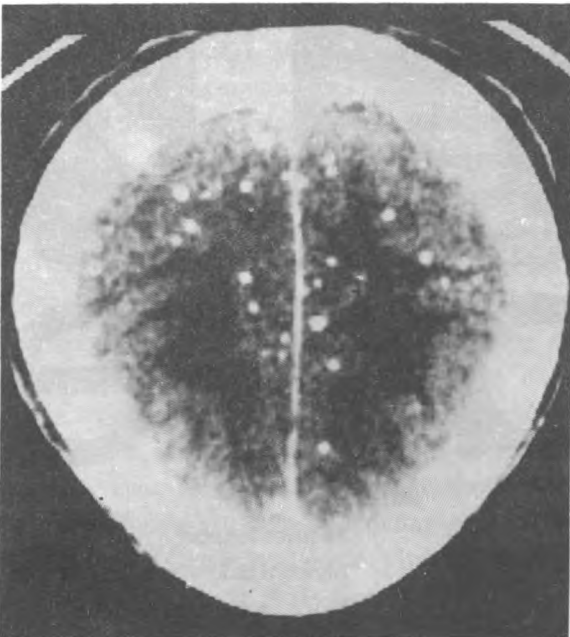
*Figure I: CT scan showing "owl eye" lesions typical of cysticercosis*



*Figure II: Multiple large parenchymal cysticerci with midline shift*



*Figure III: Multiple calcified cysticerci*



were reincubated at 37°C for 45 minutes. After washing again, 50 µl substrate (0,04 pc orthophenylene diamine in 0,2M acetate buffer, pH 5,5, with 0,6 µl 20-Vol hydrogen peroxide to each ml of substrate added immediately before use) was added to each well. Colour development was allowed to continue for 10 minutes at room temperature before being stopped by the addition of 50 µl 4N hydrochloric acid. Optical densities were read immediately on a Titertek Multiskan ELISA reader at 492nm. The delta OD was calculated as the difference between the mean of duplicate antigen positive wells and the mean of the duplicate antigen negative wells for the same serum, as described previously.<sup>11</sup>

A delta OD > 0,3 was considered positive, and < 0,2 was considered negative. Sera giving intermediate values were retested, and if the same result was obtained, they were regarded as positive but suggestive of old, inactive cysticercosis.

**Statistics:** Sensitivity was determined as the percentage sera from CT or biopsy proven cysticercosis patients giving a positive NCC ELISA.

The positive predictive value was determined as the percentage of all patients with a positive NCC ELISA whose CT or biopsy confirmed active cysticercosis. The negative predictive value was determined as the percentage of all patients with an NCC ELISA of 0.2 whose CT scan showed no evidence of active cysticercosis. While it would have been preferable to perform CT scans on all patients in this study, in order to determine specificity, this was not possible because of costs. Specificity was therefore calculated from patients with infections other than cysticercosis giving a negative NCC ELISA.

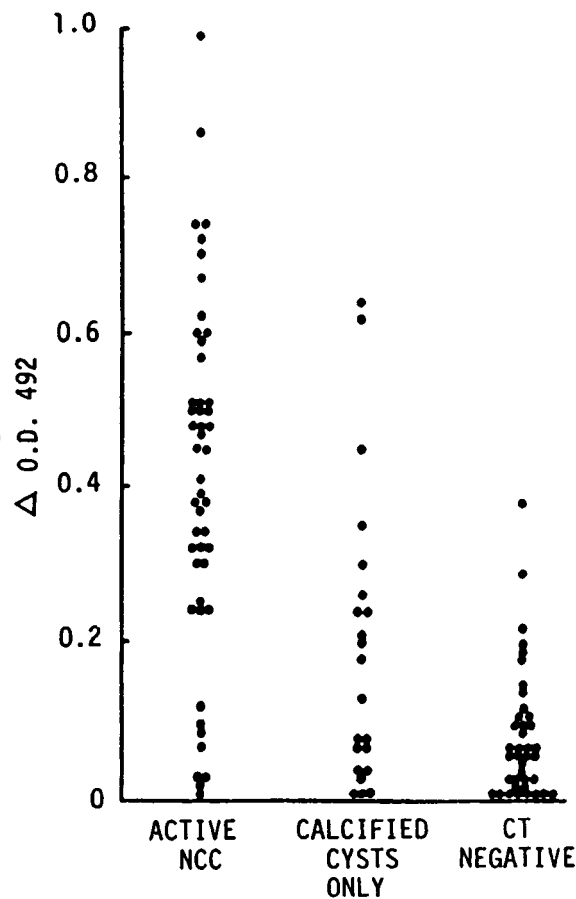
RESULTS

Over the three-year period that this study was continued, serological tests were carried out on 646 specimens from 630 patients with neurological signs or symptoms compatible with NCC. Overall, 80 (20 pc) specimens from 67 (11 pc) patients were positive (Figure IV). The prevalence was higher in men (66/377, 18 pc) than in women (10/149, 7 pc) where the sex was recorded on the request form. Among 332 patients for whom the age was given, less than 10 pc of those under 20 years were seropositive, compared with 11 pc aged 20-29, 22 pc aged 30-39, 23 pc aged 40-49 and 27 pc aged 50 years or more.

Forty-eight sera were obtained from 42 patients with CT or biopsy evidence of active NCC, and of these 40 had a delta OD >0,2 and 34 had a delta OD >0,3, giving sensitivities of 83 pc and 71 pc at these two levels. False negative serology was associated with HIV infection in three patients, but could not be accounted for in the others. Of 22 specimens from 20 patients with CT or X-ray evidence of calcified cysts only, 12 (55 pc) had a delta <0,2, four (18 pc) had a delta OD >0,3 and six (27 pc) had intermediate values. Negative serology (delta OD <0,2) was found in 35/38 (92 pc) specimens from CT negative patients, while two gave intermediate values, and one was seropositive (delta OD >0,3). The positive predictive value was thus 75 pc (40/53) at a delta OD level of >0,2 and 87 pc (34/39) at >0,3 and the negative predictive value was 65 pc (35/55) of patients with no evidence of infection at all, and 85 pc (47/55) of patients with no evidence of active infection.

None of 25 patients with intestinal hymenolepiasis, 30 patients with schistosomiasis, 30

Figure IV: ELISA serology for cysticercosis. Delta OD values for patients with active neurocysticercosis, patients with calcified cysts only and patients with negative computerised tomography scan



patients with leprosy, 21 patients with acute malaria, 30 patients with positive syphilis serology and 30 patients with pyrexia of unknown origin were NCC ELISA positive. Three of 11 (27 pc) patients with intestinal taeniasis, and each of two patients with biopsy prove hydatid disease were seropositive.

Of the 61 patients from the community epilepsy treatment study, two (3 pc) had positive serology. One had died of undetermined causes before he could be traced, and the other had calcified lesions on CT. Six (9 pc) of the 68 CT scans from the stroke study showed calcifications compatible with inactive cysticercosis, but none had active cysticerci.

## DISCUSSION

In this study we obtained evidence of active NCC in 11 pc of patients attending a neurology clinic, and in 3 pc of outpatients enrolled in a community study of seizure treatment. The frequency and seriousness of NCC and the availability of effective chemotherapy militate in favour of an active approach to diagnosis using a more effective technique than CT scanning. Our experience suggests that all patients presenting with unexplained seizures or other neurologic syndromes compatible with NCC should be tested for anti-cysticercal antibodies. Because of the high positive predictive value of the test in our setting, patients with positive serology, particularly those giving a delta OD >0,3 should be considered for chemotherapy without further diagnostic investigations.

For patients with an intermediate result (delta OD 0,2-0,3) it would be advisable to obtain CT or other evidence of active infection before commencing treatment. False positive serology appeared to be limited largely to patients with intestinal taeniasis or with hydatid disease. The former may be at risk of developing or transmitting NCC and would be treated effectively, if excessively, by the therapy for NCC. Human hydatid disease occurs so rarely in Zimbabwe as to be a rare source of diagnostic confusion. We have found no evidence of false positivity due to common parasitic or other infections.

False negative results were occasionally recorded in patients with viable CNS cysticerci, and while some of these patients were known to be HIV positive and therefore possibly immunocompromised, this was not the case in all. Failure to detect many cases of infection with inactive, non-viable cysticerci is of limited concern since these lesions do not benefit from chemotherapy.

Many studies have documented improvement or resolution of NCC lesions following treatment with praziquantel or albendazole.<sup>12-14</sup> There is clear consensus that brain parenchymal cysts, particularly those that are large and lacking in inflammatory response, benefit from treatment, but a number of issues remain controversial. A reaction ranging from headache to seizures and obtundation may sometimes follow soon after commencing anthelmintic

therapy, presumably related to the release of antigens from dying parasites.

Some authorities recommend the administration of glucocorticosteroids prophylactically while others suggest they should be used only when severe reactions occur.<sup>15, 16</sup> In children, NCC is often characterised by multiple inflammatory lesions which resolve without specific anthelmintic therapy, and the role of such therapy is thus not clear.<sup>17</sup> The efficacy of anthelmintic therapy appears to be low in basal meningitis or subarachnoid cysts,<sup>18</sup> negligible in intraventricular or intraocular cysts,<sup>19, 20</sup> unestablished in spinal cysts and, of course, absent in calcified cysts.

There is good evidence that albendazole is at least as effective as praziquantel for chemotherapy of NCC, and although the optimal dose has not yet been established, the cost of treatment is likely to be considerably lower. Because of the possibility of reactions, treatment should be commenced in hospital. Every effort should be made to obtain CT scan or neurosurgical opinion for patients with findings of raised intracranial pressure, and ventricular shunting is advised before anticysticercal treatment in patients with hydrocephalus.

In summary, NCC is a common cause of neurological disease in Zimbabwe, and serological diagnosis appears to be a useful and practical approach to diagnosis, with the ELISA test showing high specificity and sensitivity. Further studies are needed to determine the efficacy of a diagnostic strategy based on serology rather than CT, and to establish whether serology can be used to follow up patients and confirm cure.

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