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Use of affinity purified heterologous antibodies in an ELISA for the detection of *Entamoeba histolytica* in faecal specimens

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ABSTRACT

A simple and sensitive enzyme linked immunosorbent assay (ELISA) was developed to detect *Entamoeba histolytica* antigen in human faeces using an affinity purified heterologous antibody system. Antibodies purified from pooled human sera of patients with amoebic liver abscesses were used as capture antibodies and peroxidase labelled hyperimmune serum from the rabbit was used as the developing antibody. Only one stool sample was obtained from each subject. Stool samples were positive by ELISA in 117 out of 121 (97%) patients with *E. histolytica*. In addition 52 of 152 (33%) subjects with no demonstrable parasite in a single stool examination, and 39 of 141 (28%) subjects with infections other than *E. histolytica* were also positive. The ELISA was negative for amoebic antigen in 16 of the 17 (94%) stool samples from apparently healthy subjects in whom no cysts or trophozoites of *E. histolytica* were seen by microscopy in 4 to 5 stool samples. In endemic areas the ELISA is a useful diagnostic tool and can be used as a routine screening test.

INTRODUCTION

Entamoeba histolytica has a widespread distribution in tropical and subtropical areas with infection rates as high as 80%.[1–5] In spite of the introduction of new sensitive serological assays for detecting specific *E. histolytica* antibodies[6–8] and circulating antigens,[9–11] the diagnosis of invasive intestinal amoebiasis is still largely dependent upon microscopic identification of cysts and trophozoites

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of *E. histolytica* in the stool.[12] However, there are a number of problems associated with microscopic examination. Other amoebae morphologically similar to *E. histolytica* and several other agents interfere with the integrity of the trophozoites.[13,14] Even after 6 to 7 examinations, only up to 76% of the stool samples reveal the presence of amoebic infection.[14,15] Moreover, microscopic examinations require a high degree of expertise. Recently different ELISA techniques have been used to detect *E. histolytica* antigens in stool samples using multi-layer systems with immunoglobulins[16–18] and monoclonal antibodies.[19] Besides being independent of visual identification or physical integrity of the parasite, these techniques have advantages of being cost effective, rapid and easy to perform on a single stool sample. A double antibody ELISA was developed using affinity purified heterologous antibodies to find out whether it might be useful in routine screening of stool samples in endemic areas with multiple parasitic infections.

MATERIAL AND METHODS

Preparation of stool samples

The study included patients with abdominal discomfort who were seen at the out-patient clinic of the Gastroenterology department at the All India Institute of Medical Sciences, New Delhi. Each patient provided a single stool sample which was examined by the standard formol-ether concentration technique. The samples were screened for both pathogenic and non-pathogenic parasites, and were designated to be positive if cysts of *E. histolytica*, *G. lamblia*, *E. coli*, *E. hartmanni*, *Endolimax nana*, *Iodamoeba buetschlii*, *Hymenolepis nana*, Trichomonas, *Trichuris trichiura* and Ascaris were found.

A 20% extract of fresh stool samples was also prepared by mixing 2 g of stool with 8 ml 0.1 M phosphate buffered saline (PBS) pH 7.2 with a stirrer for 2 minutes and this was centrifuged at 3000 rpm for 10 minutes at 4°C. The clear supernatant was stored as a stool extract at −70°C till the ELISA was performed.

Controls

Stool samples from 17 apparently healthy subjects with no evidence of any recent or past amoebic disease were collected. In them 4 to 5 stool samples were negative on microscopy for any cysts or trophozoites. Stool extracts from these healthy controls were prepared by the method detailed above.

Preparation of E. histolytica antigen

The *E. histolytica* strain NIH-200 was cultured axenically in Diamond's TPS-1 medium.[20] After 20 hours, the amoebae were harvested by centrifugation at 1000 *g*, for 10 minutes at 4°C. These harvested trophozoites were washed three times with saline, frozen and thawed once, sonicated for 5 minutes at 20 Kcycles in an ultrasonic disruptor (MSC, UK) and finally centrifuged at 10 000 *g* for 30 minutes at 4°C. The protein content of the clear supernatant (the antigen) was determined[21] and the supernatant stored frozen in small aliquots of 0.5 ml at −75°C.

Purification of rabbit-human amoebic antibody

Antigenic protein (10 mg) from axenically cultivated *E. histolytica* was coupled to CN Br-activated sepharose 4B[22] and the protein-sepharose conjugate stored at 4°C in 0.1 M phosphate buffered saline (PBS), pH 7.2 with sodium azide (1 mg/ml). Antibodies were precipitated from rabbit serum by the addition of an equal volume of saturated ammonium sulphate. The partially purified antibodies were incubated with *E. histolytica* antigen coupled to sepharose 4B at 4°C on an end-to-end rotor mixer overnight. Excess proteins were washed and centrifuged three times in PBS at 3000 rpm for 10 minutes. Bound amoebic antibody was eluted by two incubations in 4 ml of 0.05 M diethylamine on a rotor mixer for 90 minutes, pooled and dialyzed against 0.1 M carbonate buffer pH 9.6.

Preparation of conjugate

Affinity purified rabbit *E. histolytica* antibodies were labelled with horseradish peroxidase (HRPO) (Sigma P-8375) using the two-step technique with glutaraldehyde (Sigma G-5882).[23] The conjugate was then mixed with an equal volume of distilled glycerol and stored in aliquots of 0.1 ml at −75°C. The stored conjugate was used at a dilution of 1 : 400 in 0.1 M PBS, pH 7.2 containing 10% foetal calf sera (FCS) after the optimum dilution was determined by serial titrations.

Purification of human anti-E. histolytica antibodies

This was essentially the same as that for rabbit anti-human amoebic antibody except that antibodies were precipitated with ammonium sulphate from pooled human sera of patients with amoebic liver abscesses and incubated with *E. histolytica* antigen coupled to sepharose 4B. The elution and storage procedures were identical to those followed for rabbit antibodies.

Preparation of rabbit anti-E. histolytica

Normal rabbit serum (NRS) was obtained by bleeding rabbits before vaccination. Rabbit hyperimmune sera were prepared by immunization with an axenically cultured NIH-200 strain (3 vaccinations of a rabbit with 5×10^6 amoebae—1.75 mg protein in 0.5 ml saline and 0.5 ml Freund's complete adjuvant) at intervals of 7 and 12 weeks, respectively, followed by exsanguination 18 days later.

Enzyme linked immunosorbent assay

The ELISA was carried out on polystyrene beads (6.4 mm diameter, Precision Plastic Ball Co., Chicago, Illinois). These beads were activated with a 0.25% (v/v) aqueous solution of glutaraldehyde for one hour at room temperature and overnight with affinity purified amoebic antibodies from pooled human sera at the optimum dilution of 5 μg/ml in 0.1 M carbonate buffer, pH 9.6. The beads were then washed three times with PBS containing 0.05% Tween-20 (PBS-Tween) and the additional binding sites on the surface were blocked by the treatment of beads with 0.5% gelatin in PBS overnight at 4°C. The beads were washed three times with PBS-Tween and stored at 4°C until used.

Stool extracts measuring 200 μL were incubated with

antibody coated polystyrene beads on a test plate at 37°C for 4 hours. The beads were washed with 5 ml PBS-Tween three times and 200 µL of HRPO labelled rabbit anti-amoebic antibody (conjugate) was added to each bead and incubation was carried out for a further 2 hours at 37°C. Following washing with 5 ml PBS-Tween five times, the beads were transferred to tubes. The enzyme activity was measured by the colour reaction after the addition of 300 µL of freshly prepared substrate solution (0.4 mg of o-phenylene diamine per ml of 0.1 M phosphate citrate buffer, pH 5.0 containing a final concentration of 0.06% hydrogen peroxide) to each tube containing 4 beads and incubating it in the dark at room temperature for 15 minutes. The reaction was stopped by adding 1 ml of 4N sulphuric acid and the optical density (OD) was read at 492 nm. Each sample was run in duplicate. Based on statistical analyses of samples from controls, a cut-off point equivalent to 2 standard deviations (SD) above the mean of the OD value was calculated. Any test sample with an OD value of more than the cut-off point was considered to be positive.

Tests for specificity

ELISA was performed on cultures from other parasites, where the stool extract was replaced by antigenic preparations of *G. lamblia*, *M. tuberculosis*, stool concentrates of *E. coli* and *Endolimax nana*.

In another control experiment, the beads were coated with normal rabbit serum and 31 of 141 samples with mixed infections other than *E. histolytica*, as seen by microscopic examination, were tested for amoebic antigen by ELISA.

RESULTS

Sixteen of 17 stool samples negative for *E. histolytica* by microscopic examinations from subjects in which 4 to 5 earlier stool samples were negative for any parasite showed negative ELISA results for amoebic antigen. ELISA was negative in antigenic preparations of *G. lamblia*, *M. tuberculosis*, *E. coli* and *Endolimax nana* suggesting that there was no cross reaction between these preparations and amoebic proteins. There was no difference in the results of the 31 samples tested with mixed infections other than *E. histolytica* for amoebic antigen in stool when hyperimmune serum was replaced by normal rabbit serum as the catching antibodies.

A total of 420 stool samples were screened: 121 stool samples were found to be carrying cysts of *E. histolytica* including 68 samples where the infection was mixed with other parasites. In 141 stool samples infections other than *E. histolytica* were present: *G. lamblia* infection in 41 patients, non-pathogenic *E. coli* and *Endolimax nana* in 55 patients, Ascaris and *T. trichiura* in 29 patients and other infections in 16 patients. In stool samples from the other 158 patients, no ova or cysts were seen.

Results of the ELISA are shown in Table I. *E. histolytica* antigen tested by ELISA showed a 100% reactivity when present as a single infection. However, the positivity rate was 97% when *E. histolytica* cysts were present either alone or in a mixed infection. In all, 39 of 141 (28%) stool samples positive for infections other than *E. histolytica* were found to be positive by the ELISA. In 158 stool samples where no parasite could be seen microscopically in a single stool examination; 52 (33%) showed reactivity for *E. histolytica* antigens.

TABLE I. ELISA reactivity for amoebic antigen in stool samples containing a variety of parasites by microscopic examination

Microscopic examination	Samples tested	Positive samples	
		n	%
E. histolytica	53	53	100.0
E. histolytica + *G. lamblia*	16	15	93.8
E. histolytica + *G. lamblia* + others	6	5	83.3
E. histolytica + others*	46	44	95.7
G. lamblia	37	5	13.5
G. lamblia + others	4	4	100.0
E. coli	24	10	41.7
E. nana	17	3	17.6
E. coli + *E. nana*	14	4	28.6
Ascaris	16	5	31.3
T. trichuria	10	3	30.0
Ascaris + *E. trichuria*	3	1	33.3
I. buetschlii	6	1	16.7
H. nana + others*	6	2	33.3
Trichomonas	4	1	25.0
NAD**	158	52	32.9
Total	420	207	49.3

* Other infections include *E. coli, E. nana, E. hartmani, Iodamoeba buetschlii, Hymenolepis nana* and Ascaris

** No parasite seen on microscopic examination

TABLE II. Comparison of ELISA and microscopic examination for the detection of *E. histolytica*

E. histolytica	Microscopic examination		Total
	Positive	Negative	
ELISA positive	117	90	207
negative	4	209	213
Total	121	299	420

E. hartmanni was present in seven stool specimens. Six of them, included in the group of mixed infection with *E. histolytica* and other parasites, were all positive for amoebic antigen. Since *E. hartmanni* was present as a mixed infection in most of the cases in combination with *E. histolytica* it was not possible to determine the extent of its cross reactivity with *E. histolytica* proteins.

The sensitivity of this test was 97% and it had a specificity of 70% (Table II). Its positive predictive value was 57% and the negative predictive value was 98%. The likelihood ratio for a positive test was 3.2 and for a negative test was 0.04. It had a diagnostic accuracy of 78%.

DISCUSSION

Microscopic stool examination is generally used to diagnose active intestinal amoebiasis. However, the test should be performed on fresh stool samples for trophozoites and

cyst forms, which also may be excreted variably or distributed unevenly.[15,24] Stool concentration of formalin preserved samples is useful for examination for cysts, but not for trophozoites.[25] A single specimen obtained under optimum conditions and examined carefully provides only a 33% chance of detecting *E. histolytica* trophozoites. In patients with diarrhoea, the detection rate of cysts rises to 50%.[16,26–28] It also requires a high degree of skill and patience to perform such examinations.[3]

The ELISA offers a diagnostic alternative to detect intestinal amoebic disease, and the test can be performed on a single stool specimen. Previous attempts at using ELISA to detect *E. histolytica* in stool samples have been described using either a) a single antibody ELISA system[16] where IgG antibody raised to the cultured HK9 strain of *E. histolytica* was conjugated directly to the enzyme or b) a double antibody system using specific rabbit and human antisera[17,29] and sheep and rabbit antisera.[18] These assay systems vary in specificity and sensitivity. Ungar *et al.* found indirect ELISA using both a monoclonal antibody and rabbit antisera to be highly specific.[19] However, the test had a false negative rate of 18% and it was suspected that monoclonal antibodies lack antigenic heterogeneity.[30] The sensitivity of our ELISA was 97% in detecting stool samples reactive for *E. histolytica* antigen with a false negative rate of only 3%. However, the specificity of the test was 70% with a false positive rate of 30% and an accuracy of 78%. A possible explanation for the false negative results in 4 of the 121 *E. histolytica* positive stool samples is that it might be due to the low levels of antigen or that the antigens in these specimens were not recognized by the detecting antibodies.[17] A low infection rate and microscopic misidentification could be the other possible explanations.

The present technique with a sensitivity rate of 97% is an improvement over the multi-layer ELISA technique which has a sensitivity of 65% for the detection of amoebic antigen in cyst passers.[17] Since the chances of diagnosing an amoebic infection lie between 30% and 33% after a single examination and 72% to 76% after 6 to 9 examinations,[15] there is a likelihood that the results of the ELISA may be falsely positive in relation to those of microscopic examination of a single stool specimen. This has already been demonstrated in a selected normal population from India using a multi-layer ELISA where there was a false positive rate of 15%.[17] In another study, a false positive rate of 45% was obtained.[31]

The present ELISA test, therefore, has a relevance in an endemic area as it is easy to perform, does not depend on the expertise of the person performing the test and has a high sensitivity and specificity.

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Excessive publication in the medical sciences in India

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ABSTRACT

The extent of literature proliferation in medical sciences in India was assessed by examining publication data over six years (1980 to 1985) from departments in two medical colleges, the All India Institute of Medical Sciences (AIIMS) and the Maulana Azad Medical College (MAMC), Delhi University. The departments chosen were Paediatrics and Microbiology and their publication trends and productivity compared with a non-clinical department (Biochemistry, AIIMS) and a postgraduate non-medical teaching department (Zoology, Delhi University). The productivity data (publications per scientist per year) showed that, on an average, microbiologists and paediatricians who are not full-time researchers are publishing as much as biochemists who spend a major portion of their time in research and teaching. Paediatricians and microbiologists were prolific authors with a number of them having published more than 20 papers during the study period compared with scientists in the Biochemistry and Zoology departments. The Collaborative Index (average number of scientists per paper) was also higher for both these departments compared to the departments of Biochemistry and Zoology. Categorizing the publications on the basis of a 'quality filter' and their inclusion in an international indexing service revealed that few papers from the Paediatrics and Microbiology departments were published in the journals covered by the Science Citation Index (SCI). Most papers appeared in local journals which have very little international impact. There is a need to curb excessive publication, especially in low impact journals and I suggest that the pressure on medical scientists to publish should be reduced by delinking appointments and promotions from the number of publications and considering only 5 to 10 of the candidate's best papers when applications for selection and grants are assessed.

INTRODUCTION

One factor that is common to scientists irrespective of their place of work or area of interest is the drive to expand their bibliographies. While precise estimates are not available, the growth rate in scientific publications is estimated to be about 6% to 7% per year.[1] Over two million papers are published annually and the number of scholarly journals is estimated to be doubling every 15 years to cope with this publication load. The number of abstract journals is increasing by a factor of 10 in 50 years, resulting in about one new abstract journal for every 300 new scientific journals.[2] A large number of newsletters are appearing in rapidly growing fields such as high temperature superconductivity. Newsletters provide quick information to scientists who find the normal channels of communication too slow to learn about latest developments in research.[3]

John Ziman, the distinguished philosopher of science, feels that proliferation of literature is the natural consequence of scientific progress.[4] Many others, however, consider this growth to be excessive, unnecessary and even unhealthy.[5–9] Publications have now become inextricably associated with just about everything a scientist hopes for: Scientific prestige, career advancement and national and international grants. The literature proliferation is overburdening scholarly journals, taxing the time of conscientious reviewers, slowing the process of good work from rapidly appearing in print and pushing up costs.[6] Excessive publication has hindered effective communication among scientists, who are deluged with substandard literature. Even the advanced information retrieval tools are not fast enough to sift the important from the unimportant work.

There is global awareness and concern about this phenomenon of excessive publication and selection and

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