Detection of HP10 antigen in serum for diagnosis and follow-up of subarachnoidal and intraventricular human neurocysticercosis

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Introduction: Neurocysticercosis (NC), a parasitic disease caused by *Taenia solium*, may be either asymptomatic or show a mild to severe clinical picture with intracranial hypertension. The most severe form of the disease is caused when viable cysticerci are localised in the ventricles or in subarachnoidal cisterns at the base of the skull. Detection of the secreted metacestode antigen HP10 in cerebrospinal fluid is a sensitive and specific method for the diagnosis of these severe NC cases.

Objective and methods: To evaluate the validity of HP10 antigen detection ELISA when applied to serum, using paired serum and cerebrospinal fluid samples from 116 radiologically and clinically characterised NC patients.

Results: The HP10 antigen assay exhibited a similarly high sensitivity in identifying severe NC cases from sera (84.8%) and CSF (91.3%). In contrast, HP10 antigen was rarely detected in asymptomatic or mild NC cases (3 of 57). Importantly, the HP10 antigen assay applied to serum showed high specificity (94%) when used in 126 serum samples of non-NC subjects from an endemic community with a confirmed coproparasitological diagnosis of intestinal parasitic infections. Finally, the HP10 assay also proved to be of value in the follow-up of treated patients.

Conclusion: This study confirms that detection of the metacestode HP10 antigen in serum is a useful tool for diagnosis and follow-up of patients with severe forms of NC treated with cysticidal drugs.

Taenia solium is still endemic in most countries in Latin America, Asia and Africa. When the larva is localised in the central nervous system (CNS) it causes neurocysticercosis (NC), a parasitic infection that affects approximately 10% of the inhabitants of rural communities of endemic countries.^{1–3} The clinical presentation of NC can vary from an asymptomatic to a deadly disease.⁴ One of the factors critically involved in this clinical heterogeneity is the parasite location in the CNS. Thus when the parasite is located in the parenchyma or in the subarachnoidal (SA) space of the sulci, most patients exhibit a benign clinical presentation. In contrast, when the parasite is located in the SA space at the base of the skull or in the ventricles, a severe clinical picture is presented, frequently accompanied by intracranial hypertension. The latter localisation commonly requires surgical intervention (ventriculoperitoneal shunt), and the parasites are usually less sensitive to cysticidal treatment.⁵

As diagnosis and follow-up of NC still require costly and not always accessible radiological studies, multiple attempts have been made to develop sensitive and specific immunodiagnostic tools.^{6–9} Of particular interest is the detection of secreted parasite antigens, as these only identify viable parasites.¹⁰ The most extensively tested antigen has been HP10, which includes in its structure epitopes shared by different cestodes (eg, *Taenia saginata*, *Taenia solium* and *Taenia crassiceps*).^{10–12} Recent reports have shown that HP10 detection is an indicator of the presence of vesicular cysticerci located in the SA space at the base of the skull or in the ventricles, the most severe forms of NC. HP10 detection in serum has also been reported to be useful as an indicator of the presence of vesicular parasites in hydrocephalus secondary to NC.¹³ Also, the level of HP10 antigen significantly decreases after effective cysticidal treatment, thereby reducing the number of required imaging studies.^{13–16}

This study was designed to evaluate the specificity and sensitivity of the HP10 assay in sera and compare it with antibody and HP10 detection in CSF. Paired CSF and sera samples from the same NC patients were used for these purposes. The specificity of the assay was determined based on the levels observed in the sera of inhabitants without cysticercosis from a *T solium* endemic rural community.

MATERIALS AND METHODS

Paired CSF and serum samples from hospital patients

CSF and sera were simultaneously collected from 116 NC patients at the Instituto Nacional de Neurología y Neurocirugía, Mexico City. These patients represent almost all of the subjects with NC that required lumbar puncture over a 12 month period for their diagnosis and/or follow-up. In 13 of these patients, paired CSF and serum samples were obtained before and after treatment (cysticidal drugs and corticosteroids or surgical treatment). In all cases, diagnosis was based on: clinical manifestations (presence of seizures, focal deficit and intracranial hypertension) and imaging studies (image compatible with the presence of vesicular, colloidal or calcified cysticerci). The following information was collected for each NC case from the radiological studies (CT and MRI): state of the cysticerci (vesicular, colloidal or calcified) and CNS location (SA space at the base of the skull, convexity SA space, parenchyma or ventricles).

Patients were informed that sera and CSF samples obtained during their hospital studies would be used for this work and gave their informed consent.

Abbreviations: CNS, central nervous system; NC, neurocysticercosis; OD, optical density; SA, subarachnoidal

This study had a double blind design. Neither the neurologists nor the radiologists knew the results of the HP10 test and the laboratory technicians did not know the clinical diagnosis of the neurological patients.

Serum samples from inhabitants of endemic community and from subjects with hepatic abscesses

To evaluate the specificity of the HP10 antigen detection assay, the HP10 level was determined in 126 inhabitants from a highly endemic rural community previously studied for epidemiological purposes.² All of these subjects were examined for NC by CT, and in 77, coproparasitoscopic examinations were also performed in serial faecal samples, as described elsewhere.² HP10 antigen was also measured in 25 patients with hepatic abscesses (10 pyogenic and 15 amoebic).

Detection of specific antibodies

Anticysticercal antibodies were determined by ELISA using cysticercal fluid as a source of antigens following the procedure previously described.² Samples were run in duplicate and a sample was considered positive if the mean optical density (OD) value was higher than the cut off value, which was calculated based on the mean of the OD plus 2 SD of 82 CSF (0.20) and 41 serum (0.28) samples from non-NC controls. The reproducibility of the assay was assessed based on the coefficient of variation (CV) defined as ((SD/mean)×100). The intra-assay CV was 2.6% and the interassay was 6.9%.

Detection of HP10 antigen

HP10 antigen was detected by Ag-ELISA as described previously.¹⁰⁻¹⁶ Samples were run in duplicate.

Briefly, Immulon I plates (Nunc, Rochester, New York, USA) were coated with monoclonal antibody HP10 (100 µl at 10 µg/ml in 0.07 M NaCl buffered with 0.1 M borate, pH 8.2) and left overnight at 4°C. The plates were washed four times with 200 µl/well of wash solution (0.9% w/v NaCl containing 0.05% v/v Tween 20). The plates were blocked using 200 µl diluent (phosphate buffered saline containing bovine serum albumin 1.0% w/v and 0.05% v/v Tween 20) and left for 60 min at room temperature before being washed in a similar way. Undiluted CSF or serum samples (100 µl/well) were added and incubated for 30 min at 37°C. Bound HP10 parasite antigen was detected using biotinylated monoclonal antibody HP10 (1:4000 in diluent, for 30 min at 37°C), horseradish peroxidase conjugated streptavidin (Zymed, San Francisco, California, USA) (1:4000 in diluent, 30 min at 37°C) and tetramethylbenzidine (Zymed) as substrate. The colour reaction was allowed to proceed for

30 min at 37°C in the dark and was stopped by adding 100 µl 0.2 M H₂SO₄ (Baker, Estado de Mexico, Mexico). OD (450 nm) was determined in an ELISA processor (Versamax microplate reader; Molecular Devisable, Sunnyvale, California, USA).

A sample was considered positive if the mean OD value was higher than the cut off value, which was calculated based on the mean of the OD plus 2 SD of 82 CSF (0.26) and 41 sera (0.20) samples from non-NC controls. The assay exhibited high reproducibility (intra-assay CV = 2.9%; interassay CV = 13%).

Statistical analysis

Data were processed in Excel 7.0 (Microsoft) and SPSS 10.0 for Windows. Parametric descriptions (mean and SD) were calculated. Univariate analysis of the data (Pearson's ×2 test with Yates' correction or Fisher's test when appropriate) was used to identify the differences in absorbance values between groups. A p value ≤0.05 was considered significant. Differences between mean ODs were evaluated by Tukey's post hoc test. Kappa coefficient (κ) was calculated to evaluate the qualitative concordances between HP10 results in CSF and sera. This coefficient varied between -1 and +1. The closer the value to 1, the stronger the concordance.¹⁷

Figure 1 Scatterplot indicating the ELISA optical density (OD) values obtained in the HP10 antigen ELISA using serum and CSF from the 116 patients with neurocysticercosis involved in the study (Pearson correlation coefficient r = 0.77, p < 0.0001).

Table 1 Sensitivity (%) of antibody and HP10 detection in sera and CSF of 121 neurological patients

	n	Sera		CSF	
		Ab	HP10	Ab	HP10
Confirmed neurocysticercosis cases					
Vesicular					
SA space at the base or ventricle	46†	96.5	84.8	100	91.3
Parenchyma or sulci SA space	6‡	80	0	80	0
Damaged (calcified, colloidal or *solved infection)	51§	40.4	5.9	68	3.9
Abnormal NMR**	13¶	90	30.8	90	61.5

Ab, antibody; NMR, nuclear magnetic resonance; SA subarachnoidal.
*Neurocysticercosis cases in which the cysticerci disappear after cysticidal treatment according to radiological studies.
†Detection of antibodies was made in only 29 patients.
‡Detection of antibodies was made in only five patients.
§Detection of antibodies was made in only 47 patients.
¶Detection of antibodies was made in only 10 patients.
**MRI showed an enlarged ventricle or SA cisterns caused by the presence of not distinguishable cysts or residual inflammation after cysticidal treatment.

Figure 2 Levels of HP10 parasite antigen and anticysticercal antibodies in the serum and CSF in the three groups of patients with neurocysticercosis (NC). VSAb/Ve, patients with vesicular NC with the cysts located in the subarachnoid space at the base of the brain, or in the ventricles (n = 46 for HP10 detection and n = 29 for antibody detection), VSAs/P, patients with vesicular NC with the cysts located in the subarachnoid sulci or in the parenchyma (n = 6 for HP10 detection and n = 5 for antibody detection). D, patients with dead or calcified cysts (n = 51 for HP10 detection and n = 47 for antibody detection). Solid line represents the cut off value for each group. Ab, antibody; OD, optical density.

RESULTS

HP10 antigen is detected in serum and CSF in most of the severe NC cases

Table 1 shows that HP10 was detected in 84.8% (39/46) of serum and 91.3% (42/46) of CSF samples in NC patients with vesicular cysticerci in the SA space of the base or in the ventricles, the most severe forms of the disease. Interestingly, 96.5% and 100% of these NC cases also exhibited increased levels of specific antibodies in serum and CSF, respectively. No significant differences were found in the sensitivity of HP10 and antibody detection in these severe NC cases (p = 0.2).

The HP10 antigen was not detected in serum or CSF samples from the six patients with less severe disease with parenchymal cysticerci, and was identified in only three sera and two CSF samples from treated patients in which no cysticerci were found by radiological studies. In contrast, antibodies were detected in

80% of the parenchymal NC cases and in 40.4% and 68% in sera and CSF, respectively, of patients with damaged cysticerci.

The level of HP10 antigen significantly correlated between paired serum and CSF samples (fig 1). Considering the vesicular NC cases with parasites located in the SA space of the base or in the ventricles, 39 of 46 cases were HP10 positive in sera and CSF and four were HP10 negative in both samples ($\kappa = 0.69$; $p < 0.0001$). The six vesicular NC cases with cysticerci in the parenchyma were negative in both samples, and in 48 of the 51 cases with damaged parasites, HP10 levels were negative (n = 47) or positive in both (n = 1) ($\kappa = 0.37$, $p = 0.007$). However, most of the patients showed higher levels of HP10 antigen in the CSF, with only a few cases where the reverse was observed.

Levels of HP10 in sera and CSF did not correlate with the level of CSF inflammation. In addition, no significant differences were found in the mean number of cells in CSF between NC patients who were HP10 positive or negative, in CSF or in sera.

Levels of HP10 antigen in the three groups of NC patients (vesicular in SA base or ventricles, parenchymal vesicular and inactive) are illustrated in fig 2. There was a marked difference in the levels of HP10 between the group of patients with severe NC (group 1) and the group with less severe NC (groups 2 and 3). In contrast, there was less variation in the levels of antibody detected in the three different clinical groups. Thus, in CSF, the difference was 1.86 (1.4–2.3) for HP10 detection and 0.59 (0.09–1.08) for antibody detection. Similarly, in serum, the values were 1.24 (0.8–1.7) for HP10 detection and 0.7 (0.2–1.2) for antibody detection.

High specificity of HP10 detection

To test the specificity of the assay, HP10 levels were determined in a total of 126 inhabitants of a rural community endemic for cysticercosis and in 25 subjects with hepatic abscess (pyogenic or amoebic). An increased level of HP10 was found in only nine subjects (94% specificity). Coproparasitological analyses were also performed on 77 of the patients, and at least one infectious agent was detected in 36. Increased HP10 levels were not associated with the presence of calcified cysticerci in the CNS (p = 0.54) or any of the following infectious agents: *Entamoeba coli*, p = 0.34; *Giardia lamblia*, p = 0.45 or *Ascaris lumbricoides*, p = 1). An apparently significant association was observed with *Entamoeba histolytica* (3 of 6 HP10 positive subjects were infected by this parasite vs only 6 of 71 HP10 negative subjects, p = 0.02). The relevance of this association is doubtful, however, as increased levels of HP10 were not found in a total of 15 additional patients with confirmed amoebic hepatic abscess (p = 0.5).

Table 2 Levels of HP10 antigen in CSF and serum samples taken before and after cysticidal treatment from 13 patients diagnosed with vesicular neurocysticercosis in the subarachnoid space at the base of the brain or in the ventricles

Patient No	Pretreatment		Post-treatment		Cysticercal status
	HP10 CSF	HP10 sera	HP10 CSF	HP10 sera	
1	2.48	0.43	1.42	0.17	D*
2	0.8	0.98	0	0	D
3	1.9	1.4	0.09	0.08	D
4	2.5	3.31	0.09	0.08	D
5	1	0.29	1.13	0.2	V†
6	0.88	3	0.7	2.7	V
7	1.6	0.6	2.74	1.3	V
8	1.2	1.68	2.5	2.7	V
9	1	0.2	2.7	0.9	V
10	1.1	0.08	3.2	2.9	V
11	2	1.2	3.1	1.8	V
12	2.6	1.9	2.7	1.6	V
13	1.2	1.7	4	2.4	V

*Damaged or †vesicular cysticerci. The treatment was successful in patient Nos 1–4 but patient Nos 5–13 were refractory to treatment.

HP10 antigen detection in sera: a useful tool for decision making in NC treatment

In 13 NC patients, the viability status of the cysticerci after specific treatment could not be determined by radiological studies; 90% of these patients still had antibodies in sera and CSF. However, HP10 was detected in sera in only four individuals, and in CSF in eight.

HP10 antigen detection in sera: a useful tool for the follow-up of severe NC cases

In 13 NC patients, HP10 levels were determined in CSF and serum before and after specific treatment. After treatment, the parasites disappeared or became calcified according to radiological studies in the first four patients. Table 2 shows that, in these four patients, HP10 levels dropped after treatment. In contrast, in the other nine patients in whom parasites remained vesicular, HP10 levels continued to be elevated.

DISCUSSION

In a previous study it was demonstrated that the secreted metacestode HP10 antigen level in CSF is a highly predictive factor that indicates the presence of vesicular cysticerci in the ventricles or SA space at the base of the skull.¹⁸ As the collection of CSF samples is an invasive procedure, we examined the possibility of NC diagnosis via serum HP10 detection. Using a group of 116 NC patients included over a 12 month period, we demonstrated that the HP10 antigen level in serum is an indicator of NC and is as sensitive and specific as it is in CSF. A high correlation ($r = 0.77$) was observed between levels of antigen detected in each compartment. Not surprisingly, in most cases, higher levels of HP10 antigen were found in CSF than in serum. The possibility that vesicular cysticerci localised outside of the CNS could contribute to the increased levels of antigen in serum cannot be discarded.¹⁹ However, the high specificity (94%) found in this study using sera from inhabitants of a community highly endemic for *T. solium* suggests that cases of extra-CNS cysticercosis with or without cerebral involvement are very rare. This possibility is supported by the almost total absence of subcutaneous nodules found in a screened population of thousands of subjects in a zone of high NC prevalence in Ecuador.²⁰ Thus detection of serum HP10 antigen as a possible indicator of ventricular or subarachnoidal NC could be particularly useful as a first diagnostic tool in endemic countries where the necessary imaging facilities are not available. Clearly, subsequent confirmation by imaging would then be carried out.

The effectiveness of serum HP10 antigen detection for the diagnosis of severe NC cases could be extremely useful, not only because testing serum antigen levels is a more simple intervention but also because: (a) in cases of severe NC usually accompanied by intracranial hypertension, CSF retrieval is contraindicated; (b) it is a non-invasive and useful method to support the diagnosis of severe NC when radiological studies are not satisfactory; and (c) it is a useful method for the follow-up of vesicular SA base or ventricle NC confirmed patients.

With respect to the antibody response, the most obvious correlation was that a high proportion of NC patients with vesicular cysticerci in the SA space or in the ventricles exhibited increased antibody levels. However, antibody levels remain increased several months after parasite calcification,² and they are present in NC patients, regardless of parasite location or severity. Consequently, antibody detection, although very useful for epidemiological purposes, is not a reliable indicator of active NC.

In summary, this study of an extensive and heterogeneous group of patients has demonstrated the usefulness of serum HP10 detection for the diagnosis of NC. The usefulness of the

HP10 antigen for the follow-up of treated patients with cysticerci located in ventricles or in the subarachnoidal cisterns at the base of the skull was also clearly established. These findings justify the development of a lateral flow immuno-chromatographic HP10 antigen detection assay which may be used as a screening and follow-up assay in epidemiological studies, doctor's offices and clinical laboratories.

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NEUROLOGICAL PICTURE

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FDG-PET in meningeal lymphomatosis

Figure 1 T2 weighted image shows homogenous thickening of the cauda equina extending from L1 to L5, with increased signal intensity.

Figure 2 (A) Sagittal, (B) coronal and (C) axial fused fluorodeoxyglucose (FDG)-positron emission tomography-CT images show increased FDG uptake in the spinal canal, corresponding to the magnetic resonance image.

A 45-year-old woman with biopsy proven mantle cell lymphoma in partial remission complained of headache, progressive dysphagia, dysarthria and weakness in the right leg. Neurological examination revealed left recurrent nerve palsy and weakness (4+/5) in the right extensor hallucis longus muscle.

Lumbar MRI showed irregular thickening of the cauda equina extending from L1 to L5 (fig 1). Fused fluorodeoxyglucose (FDG)-positron emission tomography (PET)-CT imaging showed increased FDG uptake (fig 2) in the spinal canal, corresponding to the lesions in the cauda equina shown on lumbar MRI. CSF demonstrated an increased number of white blood cells (23/ μ l) with normal protein and glucose levels, and cytology was positive for malignant lymphoma cells. Meningeal lymphomatosis and spinal cord metastases were diagnosed.

Intrathecal administration of methotrexate ameliorated her neurological symptoms, and CSF tests demonstrated a decreased number of white blood cells (<1/ μ l). In leptomeningeal carcinomatosis, the cauda equina are often involved because tumour cells tend to settle by gravity.¹ It is not well acknowledged that leptomeningeal carcinomatosis may be detected by FDG-PET scan, and only a limited number of case reports are available.² A case of peripheral nerve involvement in neurolymphomatosis detected by FDG-PET has been reported.³ FDG-PET may be a valuable new imaging method which allows prompt diagnosis for leptomeningeal carcinomatosis.

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