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Review article

Immunodiagnostic tools for human and porcine cysticercosis

Pierre Dorny [a,b,*], Jef Brandt [a], André Zoli [c], Stanny Geerts [a]

[a] Department of Animal Health, Institute of Tropical Medicine, Nationalestraat 155, B-2000 Antwerp, Belgium
[b] Faculty of Veterinary Medicine, Department of Parasitology, Ghent University, Salisburylaan 133, B-9820 Merelbeke, Ghent, Belgium
[c] Faculty of Agronomy and Agricultural Science, P.O. Box 222, University of Dschang, Dschang, Cameroon

Abstract

The development of improved immunodiagnostic tools has contributed to our knowledge on the importance of taeniosis/cysticercosis by enabling sero-epidemiological surveys and community-based studies to be carried out. Immunodiagnostic techniques include detection methods for specific antibodies and for circulating parasite antigen in serum or cerebrospinal fluid. The antigens used in immunoblot and enzyme-linked immunosorbent assay (ELISA) for antibody detection have evolved from crude extracts to highly purified specific fractions and recombinant antigens of the glycoprotein family, increasing both the sensitivity and the specificity of the tests. The application of ELISA for the detection of circulating parasite antigens may present some diagnostic advantages since it demonstrates not only exposure but also active infections. Until now only a few of the current techniques have been standardised and fully validated, making comparisons between studies difficult. The lack of a gold standard is a serious drawback. In surveys on cysticercosis, antibody detection systems have been useful in identifying the risk factors associated with transmission of *Taenia solium*; a high seroprevalence in a community indicates a "hot spot" where preventive and control measures should be applied. In contrast, the potential use of immunodiagnostic tools to identify cases of neurocysticercosis (NCC) in man is subject to debate. The correlation between a positive serology and neurological symptoms and/or lesions indicative for NCC on neuro-imaging techniques is poor to fair in most studies. This may be explained by the unpredictable clinical outcome of the infection and the variable immunological response of the human host to infection. A major problem is that in many developing countries, neuro-imaging methods are inaccessible and/or too expensive for the rural population at risk. Under these conditions, serology may provide the only tool for diagnosis of the infection.

Keywords: *Taenia solium*; Cysticercosis; Immunodiagnosis; Man; Pigs; Review

1. Introduction

Neurocysticercosis (NCC), the infection of the human central nervous system by the larvae of *Taenia solium*, is a major cause of epilepsy and mortality in developing countries (World Health Organization, 2002). The world map of the prevalence of the *T. solium* taeniosis/cysticercosis

* Corresponding author. Tel.: +32-3-247-6394; fax: +32-3-247-6268.
E-mail address: pdorny@itg.be (P. Dorny).

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complex has been updated considerably during the last decade. The focus is no longer only on Latin America, but also on Africa and Asia, where hyper-endemic areas have been identified (World Health Organization, 2002; Phiri et al., 2003; Rajshekhar, 2003; Zoli et al., 2003). It has become clear that this cestode is a public health problem in most developing countries where pigs are raised and pork is consumed, and where poverty, illiteracy and deficient sanitary infrastructures are common. Also, in recent years, the incidence of human cysticercosis in the industrialised north has increased as a result of increased immigration from endemic areas (Schantz et al., 1998; White and Atmar, 2002).

The development of improved immunodiagnostic tools has contributed to our knowledge on the importance of this parasite by enabling sero-epidemiological surveys and community-based studies to be carried out. Immunodiagnostic techniques include detection methods for specific antibodies and for circulating parasite antigen in serum or cerebrospinal fluid (CSF).

Serological tools may be applied on human and pigs in epidemiological studies and for diagnosis of NCC in human. The currently available sero-diagnostic tools, as well as their advantages and shortcomings are reviewed in this paper. A critical view on the use of serology in epidemiological studies, for diagnosis, and for the follow-up of cysticercotic patients is given.

2. Antibody detection methods

Infection with *T. solium* results in a specific antibody response, mainly of the IgG class. Some patients have IgM, IgA and IgE antibodies (Goodman et al., 1997), however, these subclass responses are less common than IgG (Carpio et al., 1998). It is possible that most infected hosts produce multiple antibodies of different specificities, which appear at different intervals after infection, apparently in response to the qualitative and quantitative changes in excretory, secretory and somatic antigens released during various phases of parasitic development (Schantz, 1996).

Different techniques have been described to detect antibodies to *T. solium* infections in man and pigs, such as the complement fixation test, hemagglutination, radioimmunoassay, enzyme-linked immunosorbent assay (ELISA), dipstick-ELISA, latex agglutination and immunoblot techniques (Ferreira et al., 1997; Garcia and Sotelo, 1991; Ito et al., 1998; Miller et al., 1984; Rocha et al., 2002; Tsang et al., 1989). Antigens used in these tests are either cyst fluid or crude homogenates of *T. solium* cysticerci or crude preparations of the related parasite *T. crassiceps*, which can be maintained in laboratory rodents (Pardini et al., 2002). These unpurified antigens have moderate sensitivities and relatively poor specificities (Schantz and Sarti, 1989; Fleury et al., 2001).

Research on the antigenic properties of cyst fluid and surface associated glycoproteins, and improved protein purification techniques have resulted in much more reliable serological tools (Gottstein et al., 1986; Parkhouse and Harrison, 1987; Tsang et al., 1989; Ito et al., 1998). The most specific test developed is the enzyme-linked immunoelectrotransfer blot (EITB), an immunoblot of seven cysticercus glycoproteins, purified by lentil lectin-purified chromatography, which gives close to 100% specificity and a sensitivity varying from 70 to 90% (Tsang et al., 1989). However, a sensitivity of only 28% has been found in cases with single cysts in the brain (Wilson et al., 1991). This EITB has been widely used for the diagnosis of cysticercosis in human and pig serum samples (Tsang et al., 1991). The antigen mixture is not applicable for ELISA because of the presence of non-specific fractions. In developing countries, ELISA is preferred because of its better availability, simplicity and lower cost compared with immunoblot (Rosas et al., 1986).

Recently, purification of glycoproteins from cyst fluid by single-step preparative isoelectric focusing was shown to produce very specific antigens, which are applicable both in immunoblot and ELISA (Ito et al., 1998). The specificity and sensitivity of ELISA were reported to match those of the immunoblot (Ito et al., 2002). With this ELISA, antibody responses were detectable in experimentally infected pigs harbouring 16 or more cysts (confirmed at necropsy) from 30 days

after experimental infection. The assay appears to be species-specific since pigs naturally infected with the metacestode stages of *T. hydatigena* were negative in ELISA (Sato et al., 2003).

Since the preparation of purified antigens relies on the availability of parasitic material and may be subject to the quality of this material, attempts were made to produce recombinant antigens. Different authors synthesised 10, 7–10 and 14 kDa recombinant polypeptides that can be used in immunoblot and ELISA (Chung et al., 1999; Sako et al., 2000). While the specificity of these antigens is reported to be high, the sensitivity is generally lower than with the native antigens.

3. Antigen detection methods

Antibody detection has two important drawbacks in clinical settings: (i) it may indicate exposure to infection and not necessarily the presence of an established, viable infection, resulting in transient antibodies (Garcia et al., 2001) and (ii) antibody may persist long after the parasite has been eliminated by immune mechanisms and/or drug therapy (Harrison et al., 1989; Garcia et al. 1997). In endemic villages, up to 10% or more of the general population may have antibodies to *T. solium*, not necessarily reflecting the true prevalence of cysticercosis, and leading to misdiagnosis in a proportion of neurological cases (Bern et al., 1999). Detection of anti-parasite antibodies in a patient may lead to unnecessary use of antiparasitic therapy in cases where the parasites are not viable (Garcia et al., 2000).

Antigen detection may provide a suitable alternative. It may also provide a tool for serological monitoring of anti-parasitic therapy. Several assays have been developed to detect parasite antigens, but only the monoclonal antibody-based tests directed at defined parasite antigens may ensure reproducibility and specificity (Correa et al., 1989; Harrison et al., 1989; Brandt et al., 1992; Choromanski et al., 1990; Wang et al., 1992; Erhart et al., 2002).

Antigen detection may be done on serum as well as on CSF (Choromanski et al., 1990; Garcia et al., 1998, 2000). Because of the localisation of the cysts in the brain, antigen detection in CSF may be more appropriate for diagnosis than in serum; however, sampling of CSF is more cumbersome than blood sampling.

The sensitivity of antigen detecting ELISA is reported to be high. Garcia et al. (2000) found a sensitivity of 85%, which is one of the highest recorded at present, however, in their data set only patients who were seropositive on EITB were selected. The sensitivity in patients with a single viable cyst or only enhancing lesions was 65% (Garcia et al., 2000). Erhart et al. (2002) found a very high agreement between an ELISA for detecting circulating antigen, computerised tomography scanning and biopsy examination of subcutaneous cysticerci.

Remarkably low levels of cross-reactions were observed in serum samples from a wide range of helminth and protozoan infections (Harrison et al., 1989; Erhart et al., 2002). However, the genus specificity of the tests does not allow differentiation between metacestode infections of *T. solium* and *T. hydatigena* in pigs (personal observation).

4. Validation of immunodiagnostic tests

Until now only a few of the current serological techniques have been standardised and fully validated. The variety of methods used to prepare soluble antigen from cyst material to be used in ELISA makes comparison between results difficult. Attempts have been made to validate some techniques by performing them on well-documented serum samples, yielding data on sensitivity and specificity. However, the validation of tests is hindered by the lack of a gold standard for the diagnosis of human cysticercosis. Neuro-imaging techniques of the brain cannot be considered as a gold standard because in some patients cysts may not be localised in the central nervous system. The only truly reliable gold standard for diagnosing NCC is pathological confirmation through biopsy or autopsy. Unfortunately, these procedures have obvious limitations (Carpio et al., 1998). In pigs, results of autopsy and enumeration of the cysts in the carcass may provide a tool for validation of the immunodiagnostic tests.

In the absence of gold standard, a Bayesian approach may be useful to draw assumptions about cysticercosis prevalence and test properties (sensitivity and specificity) for the test used (Pouedet et al., 2002). A Gibbs sampling programme allows the simultaneous estimation of prevalence and test characteristics, combining the prior knowledge (previous surveys, expert opinion or simply a non-informative distribution) with the present survey results to obtain the posterior distribution for each of the parameters (Pouedet et al., 2002).

5. Immunodiagnostic tools in epidemiological studies

In man, no clinical features are specific for cysticercosis, even asymptomatic brain lesions are not uncommon, and imaging methods are not available for epidemiological studies; therefore, definition of cases is based solely on immunodiagnostic methods (Flisser, 2002). In surveys on cysticercosis immunodiagnostic tools applied on human and pig, serum samples are useful in estimating the prevalence and identifying the risk factors associated with transmission of *T. solium*, a high seroprevalence in a community indicating a "hot spot" where preventive and control measures should be applied (e.g. Garcia-Noval et al., 1996; Subahar et al., 2001). Immunodiagnostic tools also offer the possibility of surveillance of the infection during and after control programmes (Garcia et al., 2000; Sarti et al., 2000; Vazquez-Flores et al., 2001).

In pigs, the benefits of immunodiagnosis are:

i) tests offer diagnosis on live animals;
ii) blood sampling followed by serological testing is more sensitive than the classical tongue examination; and
iii) the tests are relatively inexpensive and easy to perform on large numbers of serum samples.

However, there are some problems related to serodiagnosis in pigs:

i) It has been reported that the sensitivity of the available techniques is low in pigs with low levels of cyst burdens (Sciutto et al., 1998), although other authors (Nguekam et al., 2003) were able to detect pigs harbouring one single cyst using an Ag-ELISA;
ii) when measuring antibodies, antigen exposure is measured rather than actual infection;
iii) interpretation of seropositive results in young pigs may be complicated by the fact that maternal antibodies transferred by colostrum from a seropositive sow to its piglet may persist for up to 7 months. This has to be considered in studies that examine the prevalence of cysticercosis in pigs (Gonzalez et al., 1999);
iv) as in human, the problem of transient antibodies may have to be considered also in pigs, i.e. a transient antibody response to a *T. solium* infection without the establishment of a patent infection; and
v) cross-reactions with *C. tenuicollis* are rather the rule than the exception in most antibody and antigen detecting tests (personal observation).

In man, the occurrence of a transient antibody response in *T. solium* infection in field conditions was found to be a major contributor to the overestimation of the prevalence of cysticercosis in endemic areas. Review of longitudinal serologic data from serological surveys in endemic areas of Peru and Columbia demonstrated that about 40% of seropositive people was seronegative when resampled after 1 year (Garcia et al., 2001).

6. Serum antibody and antigen detection in the diagnosis of NCC patients

Serological tests may also be used for the diagnosis of cysticercosis. They can be applied both on serum and CSF. Depending on the viability and the localisation of the cysts in the brain testing on either serum or CSF may be more sensitive (Correa et al., 1989; Zini et al., 1990).

Serological tests can be very useful for confirmation of imaging techniques for differential

diagnosis of other "cyst forming conditions" including echinococcosis, brain tumours and tuberculosis (Chang et al., 1988; Del Brutto et al., 1996).

In contrast, the potential use of serology to identify cases of NCC is subject to debate.

A correlation between positive serology and neurological symptoms and/or lesions indicative for NCC by imaging techniques is poor in most studies (Ramos-Kuri et al., 1992). This may be explained by the unpredictable clinical outcome of the infection and the variable immunological response of the human host to infection. Clinical manifestations of NCC are diverse because of variable number, size and location of lesions, and immune reaction of the host (Garcia and Del Brutto, 2000). Serology and imaging techniques measure different aspects of the disease and may disagree in some patients. For instance, non-neurological infections (e.g. subcutaneous or intramuscular localisation) may have positive serology but normal brain imaging (Erhart et al., 2002). In contrast, individuals with only inactive lesions or those with a single cerebral lesion causing clinical symptoms may test seronegative (Ohsaki et al., 1999; Wilson et al., 1991). Nevertheless, the general opinion is that consistent diagnostic criteria of NCC should be based on combined neuro-imaging studies, serological tests, clinical presentation and exposure history.

Several studies have shown that high seropositivity rates for cysticercosis are significantly associated with tapeworm carrier clusters and that seropositive persons are significantly clustered within households, particularly, in households in which a member reported a history of having passed tapeworm proglottids, as well as with individuals with a clinical history of seizures (Diaz Camacho et al., 1991; Sarti et al., 1992). Immunodiagnosis is useful in identifying cysticercosis cases in tapeworm carriers and in family members of tapeworm carriers and patients with NCC. Clinical symptoms of NCC generally occur as a result of an inflammatory reaction around cysticerci, and are in this stage usually associated with degeneration of the cysticerci (Garcia and Del Brutto, 2000). Early diagnosis of NCC by serology may, therefore, provide opportunities for the prevention of clinical symptoms.

Another practical application of serology in human cysticercosis is the follow-up of the treatment. ELISA for the detection of circulating parasite antigens is a promising technique for monitoring the success of treatment of NCC patients because of the excellent correlation between the presence of circulating antigen and viable brain cysts (Garcia et al., 2000; A. Zoli, unpublished observations). Ag-ELISA results became negative 3 months after start of treatment that proved successful. In addition, it is much cheaper and accessible than neuro-imaging.

7. Conclusions

It is clear that the improvement of immunodiagnostic tools for cysticercosis has greatly contributed to a better understanding of the prevalence and the epidemiology of the infection. Immunodiagnostic tests will also provide a valuable tool in measuring the impact of the disease on pig production and on human health, data that are still missing in most endemic areas. They may contribute to the diagnosis of NCC and the follow-up of treatment. However, because of the polymorphic clinical manifestations of NCC, it would be unrealistic to claim that they can replace neuro-imaging for the clinical management of NCC. Anthelmintic treatment of epileptic patients, that have a positive antibody or antigen serology without a CT scan or MRI examination, is considered to be very hazardous. A major problem is that in many endemic countries, neuro-imaging methods are inaccessible and/or too expensive for the rural population at risk. In these conditions, serology may provide the only tool for diagnosis of the infection. Finally, efforts should be made to make cheap, reliable and standardised tools more widely available.

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