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Immunologic problems in the diagnosis of human cysticercosis

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Summary.

Two types of *Cysticercus* are found in manin : *C. cellulosae,* the most frequent, and *C. racemosus.* Antigenic differences have been observed between them being a possible cause ot false negative serology when using *C. cellulosae* only. A purified antigen of *C. cellulosae* must also be tested against sera of other parasitic diseases to eliminate cross reactions as well as against host antigens sometimes incorporated by the parasite and which may be also a source of error.

Résumé.

Problèmes immunologiques dans le diagnostic de la cysticercose humaine.

Deux espèces de *Cysticercus* ont été observées chez l'homme à Mexico : *C. cellulosae,* le plus fréquent, et *C. racemosus.* Ils présentent entre eux certaines différences antigéniques, peut-être responsables de fausses réactions sérologiques. Un antigène puritié de *C. cellulosae* doit être testé sur des sérums de porteurs d'autres helminthiases, pour éliminer les réactions croisées, et débarrassé des antigènes de l'hôte éventuellement incorporés par le parasite.

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The purpose of this paper is to analyse the host-parasite relationship in cysticercosis to visualize the immune response of the host at different times of infection ; a clear understanding of this relationship is basic for the development of a better serologic test to be used in the diagnosis of human and animal cysticercosis.

Cysticercosis is recognized as an important medical, sanitary, veterinary and economic problem in countries where the cestode *Taenia solium* is prevalent. Autopsy records during a period of 6 years in Mexico City have shown that 1.9 % of deaths are caused by this disease ; the parasite was found in 3.5 % of autopsies (1) and it is the second most frequent cause of death among parasitic disease in Mexico (2). It is a serious medical problem because brain and ocular cysticercosis produce disability and require expensive medical and surgical care ; over 40 % of cases with neurological symptoms have a bad prognosis due to limited therapeutic resources and diagnostic procedures (3).

In México, 1 to 4 % of slaughtered pigs have to be discarded because of this disease, causing important economic losses (4, 5). In other countries, for example South Africa, Chile and Poland (6, 7, 8), cysticercosis is also a serious veterinary and public health problem.

Early diagnosis of the disease in animals has been difficult so far, and only highly infected animals are detected and discarded by routine meat inspection ; therefore, undiagnosed slight infections continue transmission. A simple diagnostic test would avoid the economic losses of maintaining and slaughtering infected animals, and permit their systematic elimination to interrupt transmission of the disease.

The most viable diagnostic procedure could be a simple serologic test, in which a suitable antigen is used for hemagglutination or latex particle agglutination.

In a number of cases of cerebral cysticercosis, diagnosis is made during or after surgery. As surgery is not always indicated, a reliable serologic test is also necessary in the human disease. As the disease is frequently a symptomatic (1), a good serological test would also allow precise epidemiological surveys. Similar tests using purified antigens have been used succesfully in echinococcosis (9) and other parasitic diseases.

To date the most commonly used method for the diagnosis of human cysticercosis is the complement fixation test in spinal fluid ; however, approximately 36 % of proven cases give a negative reaction (10). A hemagglutination reaction with a crude antigen has also been used ; it has given good results in human sera, but has been unsensitive in spinal fluid, and this is important to assess brain cysticercosis (10). One limitation of these methods may be attributed to the use of a crude extract of *Cysticercus cellulosae* from hogs as antigen, but there are several other considerations to be made.

The initial response of the host to *Cysticercus*, both in man and the hog, is against antigens of the oncosphere. Gemmel et al, have shown that activated embryos of *Taenia hydatigena* and *T. ovis* are capable of protecting sheep against oral reinfection, demonstrating specific acquired protective immunity (11, 12). It is therefore possible to develop a reaction to detect these antibodies, which could be the best diagnostic

method since this is an obligatory phase of the infection. The main difficulty is in obtaining sufficient amount of oncospheres to prepare the antigen. It is also known that viable cysticerci live several years in the host, so the initial antibody response against oncosphere antigens may fall below detectable levels making such a test useful only during the initial phase of the infection.

It is not known whether the cysticercus and the oncosphere have common antigenic determinants ; if so, the preparation of a purer antigen of *Cysticercus* would make the development of such a test much casier, since viable cysticerci are abundantly obtained from infected meat. It is necessary to study the antigenic mosaics of the oncosphere and the cysticercus to search for common antigens.

Serologic tests for cysticercosis are made with antigens prepared from somatic components. So far somatic antigens of *Cysticercus cellulosae* are obtained by acetone treatment and saline extraction ; this method does not solubilize all antigenic materials ; other methods of antigen extraction, as treatment with detergents, sonication and enzymes should therefore be explored, since these have been useful for example in obtaining histocompatibility antigens (13). Another cause for a poor serologic response to *Cysticercus* test antigens may be that the host response during natural infection is directed mainly to E.S. antigens (excretions and secretions). Rickard and Bell (14) have recently shown that effective immunizing antigens are produced early in the development of the larva of *Taenia ovis* and *T. taeniaformis ;* direct contact between the host and parasite is not necessary, since the immunity is induced by activated embryos enclosed in diffusion chambers in the host. One of us (F.B.) has obtained E.S. antigens of cysticerci by maintaining live parasites from the hog in a protein free culture medium ; a subsequent purification of the excretions and secretions thus obtained could be tested for diagnostic purposes. A striking feature of cysticercosis is that viable parasites are almost always free of a surrounding inflammatory reaction in the host tissue and usually asymptomatic (15). This lack of host response could be related to poor antigenicity of the parasite wall in contact with the host.

The localization of live cysticerci in humans may also be a determining factor in false negative serologic tests. By the same token, in brain parenchyma it is known that immunocompetent cells do not have access to antigens beyond the cerebrovascular barrier, and foreign antigens transplanted to this organ are not rejected, as was shown by Medawar (16). The immunological system may not have access to cysticercal antigens located in the central nervous system, so that the individual may not become sensitized to the larval form of the parasite, particularly if the membrane antigens change during the development of the larva. For this purpose, antibody titers have to be compared between patients with parasites in brain parenchyma, brain ventricules or outside the central nervous system.

The number of cysticerci is probably an important factor in the magnitude of the host immune response. One parasite may not be capable of stimulating a detectable antibody response. On the other hand, a massive number of parasites as is usually found in animals, may stimulate a better response ; however, circulating antibodies may be constantly absorbed by the live parasites. The possibility that the parasite is

capable of digesting such antigen-antibody complexes must also be considered ; similar defense mechanisms in parasites have been described in *Entamoeba* (18).

It is known that death of the larva in the central nervous system produces a severe inflammatory reaction and is frequently accompanied by severe symptomatology. The inflammatory response is accompanied by the entrance of immunocompetent cells to the dead parasite so the host can become sensitized to those denatured somatic antigens. A subsequent antigen-antibody reaction may be responsible for the severe vasculitis of the Arthus type which is observed in such lesions (17). The factors involved in death of the parasite are not known, it may take several years and so far, there is no evidence that the host immune response plays a role.

To detect antibodies against denatured antigens of the parasite it will be necessary to prepare extracts from dead cysticerci and test them against sera of infected hosts with live of dead parasites.

Calcified cysticerci are easily detected in humans by X-ray examination ; it is assumed that the antigenic stimulus has ceased in these individuals and antibody levels are below detectable titers. There is no solid information on the longevity of *C. cellulosae* in man, on how long it takes a dead parasite to become calcified and the reaction to become negative.

In humans, two types of *Cysticercus* are found : *C. cellulosae* which is more frequent and *C. racemosus,* a peculiar larval form which does not have a scolex. One of the authors (F.B.) has observed antigenic differences between them, this being a possible cause of false negative serology when using only *C. cellulosae* as antigen. A comparison of the antigenic mosaic of both types of larva is necessary to evaluate such differences.

Finally a purified antigen of *C. cellulosae* must also be tested against sera of other parasitic diseases to eliminate cross reactions due to common antigenic determinants.

Parasites incorporate host antigens, so, the purification process should also contemplate the elimination of such antigens, which may be a source of error.

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