Epidemiology: Open Access
ISSN: 2161-1165

Vielma et al., Epidemiol 2014, 4:3
DOI: 10.4172/2161-1165.1000156

Review Article Open Access

Neurocysticercosis: Clinical Aspects, Immunopathology, Diagnosis, Treatment and Vaccine Development

José Ramón Vielma[1,3], Haideé Urdaneta-Romero[2], Juana del Carmen Villarreal[1], Luis Alberto Paz[1], Luis Vicente Gutiérrez[1], Marylú Mora[3] and Leonor Chacín-Bonilla[4*]

[1]*Laboratorio de Análisis Químico (LAQUNESUR), Universidad Nacional Experimental Sur del Lago "Jesús María Semprum" UNESUR, Santa Bárbara de Zulia, estado Zulia, Venezuela*

[2]*Instituto de Inmunología Clínica (IDIC), Facultad de Medicina, Universidad de Los Andes, Mérida, estado Mérida, Venezuela*

[3]*Laboratorio de Neurobiología, Centro de Investigaciones Biomédicas, Instituto Venezolano de Investigaciones Científicas (CIB – IVIC), Maracaibo, estado Zulia, Venezuela*

[4]*Instituto de Investigaciones Clínicas "Dr. Américo Negrette", Facultad de Medicina, Universidad del Zulia, Maracaibo, estado Zulia, Venezuela*

[*]**Corresponding author:** Leonor Chacín-Bonilla, Instituto de Investigaciones Clínicas "Dr. Américo Negrette", Facultad de Medicina, Universidad del Zulia, Maracaibo, Venezuela, Tel: +58-414-652-4576; Fax: +58-261-759-7247; E-mail: leonorbonilla42@yahoo.com

Received date: January 26, 2014; **Accepted date:** April 27, 2014; **Published date:** April 30, 2014

Abstract

Neurocysticercosis (NCC) is defined as human parasitism caused by Taenia solium in its larval stage, when the parasite is located at the central nervous system of the human beings. This disease represents a serious public health problem in developing countries. Neuroimaging studies are usually abnormal, but in most cases, not pathognomonic. Serological diagnosis of NCC is made by means of tests using crude antigens or semipurified fractions of T. solium cysticerci or the use of recombinant antigens that have improved the sensitivity and specificity of the diagnosis. Treatment of NCC is based upon the use of cystocidal drugs, namely: praziquantel and albendazole. Some vaccines to prevent porcine cysticercosis are in advanced stages of investigation, but they are not to be used in humans. Nowadays, the T. solium genome sequence will allow to create a rational design of new healing and preventive drugs. A vaccine for human taeniosis use could be developed in a short term. The aim of this review is to describe the most important clinical aspects of the NCC with emphasis in immunopathology and immune diagnosis.

Keywords: Neurocysticercosis; Taenia solium; Immunopathology; Serological diagnosis; Treatment; Vaccines

Introduction

There are two types of pathologies caused by Taenia solium infection. The first one is taeniosis, which is caused by the adult parasite that develops exclusively in human intestine. The second one, deals with the infection caused by the larval form, named Cysticercosis (CC). Cysticerci develop in the skeletic muscle, the subcutaneous tissue, and mainly in the central nervous system (CNS), where they lead to a clinical pleomorphic disorder known as neurocysticercosis (NCC) [1-6]. This is the most frequent parasitic disease of the CNS, it also can infect the eyes (ophthalmic cysticercosis), where the larvae can lodge in the retina or in the vitreous humour [2,4,6,7].

The World Health Organization (WHO) estimated more than 2.5 million people are infected with T. solium around the world, and 50 thousand deaths a year can be attributed to NCC [8]. Neurocisticercosis is a reportable disease at the international level [9] due to the impact on developing countries around the world. Cysticercosis is frequent in Latin America, Africa, and Asia, where it is considered as a poverty indicator [10,11].

In Latin America, it is estimated that there are 400,000 people with symptomatic NCC [12,13] and that 18% to 50% of epilepsy cases in adult population are caused by the disease [7,14-17]. In Brazil, prevalence rates of 72 / 100 000 and 96 / 100 000 were reported from two localities of Sao Paulo State [18]. In Peru, different seroepidemiological studies indicate a prevalence of 10-20% of CC / taeniosis in the general population and values two to three times higher in individuals with epilepsy. The main endemic areas are Sierra, North Coast and the High Jungle. NCC is present in low proportion in other zones of the country, with the area of Iquitos, apparently free of the disease [19]. In Colombia, in two rural communities of Antioquia, the prevalence of human CC was 1.2% and 2.2%. These results show that CC is endemic in this area [20]. In Venezuela, although intestinal parasites are very frequent [21-25] and tend to persist [24], very low infection rates, < 1%, of Taenia sp. have been reported [23,25-32]. However, these percentages migth be underestimated due to the low sensitivity of examining single stool specimens. A report documents high circulating T. solium metacestode antigen (64.7%) and anti - parasite antibody seroprevalence of 79.4% in an Amerindian community from the Amazonas State. As the IgM was the predominant antibody class, the findings strongly suggest the recent exposure to T. solium of this population [10]. In three rural communities from Lara and Carabobo States, prevalences of 5.7 - 9.1% were established [11]. The detection of IgG antibodies showed that the exposure to the parasite was 4-36.5%. These findings suggest that there are CC active focal points in Venezuela with a high risk of disease transmission. In Ecuador, a high rate of seropositivity of CC among urban, individuals was found in a region endemic for T. solium was 12% of the case family members and 4% of the control family members by the using the enzyme-linked inmmunoelectrotransfer blot (EITB) assay [33]. In Guayaquil City, in NCC patients admitted in a hospital from Guayaquil, prevalences of 6.4%, 2.7%, and 3.5% were noted from 1982 to 1991, 1992 to 2001, and 2002 to 2012 respectively

[34]. In La Habana, Cuba, a very low frequency of 0.01% was found in a retrospective study of neurological patients over 25 years up to 1989 [35]. In Mexico, an incidence of 0.8 cases per 100 000 per year was reported [36]. In epidemiological studies of CC conducted in Tepetzintla, Puebla State in 2001 [37] and in Cuentepec, Morelos State in 2003 [38], the same infection rate of 9.1% was found.

In developed countries, NCC has impact on public health by the large number of immigrants coming from endemic areas. In the last years, the number of cases has increased which turns CC/NCC into an emerging pathology in some developed countries [39-43].

Clinical Aspects

NCC is a complex disease; its symptoms depend on the number, type, size, localization and stage of development of cysticerci in the CNS and meninges, as well as on the degree of inflammatory response, and the host conditions [2,4,5,12,14]. In 70-90% of patients with NCC, the most common symptom is seizures, and in countries where the disease is endemic, there are a lot of cases of epilepsy in adults whose underlying cause is the CC [5,14,44]. When cysticerci lodge within the ventricular system the acute Intracranial Hypertension (ICH) secondary to Hydrocephalus (HC) may develop. Cysts in the subarachnoid space may invade the Sylvian fissure and grow to large sizes. The giant cysts formed; cause ICH with hemiparesis, partial seizures or other focal neurological signs. The most severe but less frequent of the NCC clinical presentation is due to the racemose cysticercus, with the presence of multilobular cysts, located in the ventricular and subarachnoid spaces, with a marked obstructive HC and arachnoiditis that may threaten the life of the patient. Racemose cysts in the basal cisterns can cause an intense inflammatory reaction, fibrosis, and progressive thickening of the leptomeninges at the base of the brain. Ventricular and basal cisternal locations are considered to be malignant forms of NCC. There is a high mortality rate (50%) when the HC secondary to cysticercotic meningitis is present. Most patients can die within two years after Cerebrospinal Fluid (CSF) shunting [44].

From a clinical standpoint has been established in the following clinical profile in HC in patients with NCC: males, 21-50 years old, ICH was observed in all patients, headache (HA), the CSF syndrome of NCC was detected in 31/47 patients (65.9%), Meningoencephalitis (ME), Psychiatric Disorders (PD). Computed Tomography (CT) scans showed cystic lesions, diffuse cerebral edema, and calcifications. Shunts were inserted in 41/47 (87.2%) patients. Evolution was satisfactory in 24 (51.1%) patients and fatal in 15 (31.9%) [45].

NCC can be active or inactive. The active form is associated with living parasites that cause arachnoiditis, HC, and cerebral stroke. In addition, patients can present a mass effect due to the presence of large cysts which can appear at spinal and intraventricular levels. Inactive NCC presents parenchymatous calcifications or meningeal fibrosis [2,4,13,17].

Clinical and epidemiologic aspects of children and adults with NCC

The Brazilian patient presents an overall clinical and epidemiological profile for the inactive form of the NCC: men of 31-50 years old, complex partial seizures, rural origin, calcifications visible on the CT scan, the protein increase in CSF or normal values. The severity profile corresponds to the active form of the NCC: women, urban origin, 31-40 years old, typical CSF syndrome or alterations of two or more parameters, ICH, vascular HA, and the CT scan shows vesicles or calcifications [18]. In Campina Grande and others cities of Paraba State, 44 patients with NCC had an average age was 20.6 + 14.3 years old, with male predominance. The 86.2% came from the urban area. The initial symptom was convulsion, accompanied by a lower proportion of HA. The epileptical form predominated over the combined form. CT scans showing calcification, integral cysts, degenerating; isolated or associated. The evaluation of CSF showed alterations, pleocitose linfomonocitary predominating in 100% of the cases, and positive immunological reactions in 64.3% of them [46]. In Bocatu region, Morales et al. [47] emphasized the need to consider the NCC in the differential diagnosis of children from endemic areas with symptomatic with learning disabilities, behavioral changes, and psychomotor involution. The diagnosis of NCC in 25 children took into account epidemiological, clinical, laboratory (CSF), and CT scans. From the epidemiological point of view, predominated men, of urban origin with an age range of 1-11 (average= 8 years + 6 months). The more frequent manifestations were epileptic seizures, HA, learning disability, behavioral changes, psychomotor involution, and ICH. The neurologic examination was normal in 80% (of the 25 patients, 43.4% had remission and 47.8% had improvement) allowing infer a spontaneous resolution of NCC in this patients, without the need for cystocidal treatment.

In Peru, Maldonado et al. [48] in a case-control study realized in 41 patients with a convulsive status epilepticus demonstrated of principal clinic-epidemiologic characteristics in adults attended in a National Hospital from Lima-Peru in a period of four years. Among the most important findings are: 68.3% were male, 28.6% had age between 20 and 29 years old and 15.5% resided in endemic areas of NCC. The more frequent aetiologies were remote symptomatic secondary crisis to cranio encephalic trauma and NCC and idiopathic; 26.8% showed some intercurrent infection; while, mortality was of 7.3%. Factors associated with a convulsive status epilepticus were the abrupt interruption or suspension of drugs used for the control of convulsions (p=0.038), chronic intake of alcohol (p=0.030) and irregular antiepileptic treatment (p=0.006). These authors conclude that aetiologies more frequent in the hospital studied from Lima-Peru are remote symptomatic secondary crisis to cranio encephalic trauma, neurocysticercosis and idiopathic. The irregular antiepilepticus treatment constitutes a risk factor to convulsive status epilepticus.

In Ecuador, Goodman et al. [20] demonstrates a high rate of seropositivity of CC among urban, middle to upper-middle class individuals in a region endemic for T. solium in Ecuador. The authors compared in a case-control study realized in the city of Cuenca, the rate of seropositivity used the EITB assay among family members of patients diagnosed with NCC by CT compared with family members of controls who had a negative CT scan. That seropositivity was not related to age. No neurologic symptom proved predictive of serostatus and the only demographic variable that correlated with seropositivity was increased crowding. Positive serology in index cases did correlate with CT findings as follows: 86% of patients with active lesions, 67% with transitional lesions, and only 41% of patients with inactive lesions were positive by the EITB assay. Eighteen percent of family members with a positive EITB test result had parenchymal lesions on a subsequent CT scan.

In Cuba, the correlation between disease and epilepsy (4 of 5 cases) was assessed. The main symptoms were analyzed: the three most important, in order, were tonic-clonic convulsions, HA and motor deficit respectively. The epileptic seizures were classified as secondary

generalized partial seizures (symptomatic partial epilepsy secondary to CC). The clinical form, when the site is considered, was inactive, with intraparenchymatous and meningeal (mixed) calcifications in one case [22,49].

In Venezuela, a report of 28 cases of NCC was presented, where 75% of the patients were male, aged between 30-50 years old, 57% of which came from the Capital District and the Central States (Miranda, Carabobo, and Aragua) and 14% of the Andean States (Mérida, Táchira, and Trujillo). Among the most important symptoms were presented: IHC, seizures and focal signs. All cases with neurological symptoms had an intraventricular and / or meningeal location. Pleocytosis at the expense of lymphocytes in the CSF was observe [50].

Immunopatholgy

The symptoms of the disease are a result of the granulomatous inflammatory process associated to the immune response against the parasite. In the murine model the response of the helper CD4+ T cells, Th1, seems to be decisive in the disease immunopathogeny and in the parasite elimination from the tissues. A marked predominance of interferon-gamma (INF-γ), interleukin-2 (IL-2), and minimal quantities of interleukin- 4 (IL-4), were found in early evolution injuries, by using in situ hybridization on granulomas removed from the peritoneal cavity of infected mice with T. crassiceps cysticerci. Also, a progressive increase of IL-4 levels was observed in the late stages of the disease. This could indicate a process of low regulation of the initial Th1 response [51].

The Evans Blue (EB) vital diazo dye, very soluble in water and easily linked to albumin, has been used in pigs to determine the extent of the immune inflammation around the brain cysts in NCC. The EB dye was injected to 11 naturally infected pigs with T. solium cysts to identify the degree of alteration of the blood brain barrier. A total of 369 cysts were recovered from the brains and were classified according to the color of their capsules as blue or undyed. The proportion of cysts with blue capsules was significantly higher in the pigs that received treatment 48 and 120 h before the EB infusion, indicating a greater commitment of the blood-brain barrier due to therapy. This finding is particularly important because it allows to infer the commitment of the blood-brain barrier and the degree of inflammation after treatment in patients with NCC [52].

The immune response against T. solium antigens is responsible, on the one hand, for the infection control; on the other, for the damage or injury caused to the host tissues. In human beings, inflammatory response against viable cysticerci is minimum. However, a loss of modulating the host immune response against parasite antigens with degenerate cysticerci is observed later. In this case, an intense inflammatory response has been noted with the presence of eosinophils, plasma cells, B and T lymphocytes accumulations and macrophage phagocytosis inside the destroyed cysticerci [53-57]. The serological assays that detect IgG in serum and CSF of patients with NCC, has shown a long- term humoral response. Nonetheless, cellular response is less known [43,58-67].

Sciutto et al. [68] emphasize that the high relevance of mast cells (MC) found in the brain of NCC patients is an interesting finding. These MCs express both tryptase - chymase enzymes and where found infiltrating the meninges and the brain parenchyma around vesicular and calcified cysts and in the perivascular area of the brain blood vessels. The authors pointed out that these cells could importantly contribute to the parasite destruction by modulating the local immune inflammation, possibly through a differential profile of cytokines secreted by the different MC protease phenotype [68-70]. It has been demonstrated that severe NCC patients exhibit a higher percent of T regulatory cells (Tregs) in CSF and the periphery. The increase in central and peripheral Tregs is accompanied by decreased in activated T cells in the peripheral proliferative response induced by cysticercal antigens and concanavalin A (ConA). The inflammatory conditions in NCC are associated with gonadal impairment in both male (low testosterone and estradiol levels) and female patients (low progesterone and estradiol levels), as with adrenal dysfunction resulting in reduced levels of androstenedione (A4) and dehydroepiandrosterone (DHEA) [68].

Lymphocytes TCD4+ / TCD8+ proportion is associated to the functionality of the immune system. This proportion seems abnormal in patients with NCC, with an increase of CD8+ T cell subpopulation suggesting that there is a diminished immune response. It is not known yet if the parasite is the cause or the effect of the immunodepression. Th1 / Th2 paradigm in NCC has not been totally elucidated yet. Th1 cytokine pattern seems to be related to protection. Whereas, Th2 cytokine pattern appears to be connected to disease outcome. High interleukin - 6 (IL-6) levels in CSF of patients with subarachnoid NCC are observed in the acute phase. Tumor necrosis factor - alpha (TNF-α) has been detected in children with active NCC, unlike control groups and children with inactive NCC, where TNF-α has not been detected. Cytokine response to the treatment with praziquantel shows a predominance of Th1 (high IL-2 levels in patients with NCC). This is different from the Th2 pattern against T. solium viable cysticerci in diverse animal models [67,71-76].

High levels of eotaxin and interleukin- 5 (IL-5), both eosinophil selective mediators, have been quantified in sera from patients with NCC. These cytokines are involved in the local and systemic recruitment of eosinophils. The presence of these cells as the first defensive line against parasites has been reported in porcine CC after treatment and vaccination. This suggests that eosinophils may play an important role in the degenerative phase of the infection. There are few immunohistochemical studies upon the inflammatory response against T. solium cysticerci in granulomas in the human CNS. Studies suggest the participation of Th1 and Th2 cytokines in granulomas derived from patients with NCC [77-82].

For therapeutic pourpose, it is not convenient to interfere with the inflammatory response against the parasite in NCC. Anti - inflammatory drugs are kept for very specific cases presenting severe and persistent inflammation with diffuse encephalitis and / or basal meningitis, and ICH [76].

Seizures, substance p, and edema perilesional in patients with calcified neurocysticercosis

Substance P (SP) is a neuropeptide within the tachykinin family produced by endothelial cells, neurons, and immunocytes such as lymphocytes and macrophages. Robinson et al. [83] established that SP is the epileptogenic agent in NCC in human and murine models. SP signaling is involved in nociception [84] and neuropathic inflammation. By immunohistochemistry on brain tissue specimens from patients with and without NCC, the SP peptide expression was readily detected within cells adjacent to parasite remnants in the 5 NCC brain biopsy specimens. In contrast, no SP+ cells were found distant from the parasite in the NCC biopsy specimens that included sufficient brain tissue. Autopsy specimens from patients without NCC

displayed no SP+ staining cells [83]. In NCC the calcified lesions are the most common cerebral finding because they accumulate in the brain and are a measure of prior infections. There is increasing evidence implicating calcified NCC in the genesis and / or maintenance of seizures and epilepsy in endemic populations [85]. Perilesional brain edema associated with calcified lesions is a recently described phenomenon [86]. Even now, symptomatic patients with perilesional edema around calcifications are commonly misdiagnosed as refractory NCC and unnecessarily treated with antihelmintics or even subject to brain biopsies. Perilesional edema was present in 34.5% of patients with only calcified lesions who presented seizures [87].

Nash et al. [88] realized the first prospective study of the incidence and clinical significance of perilesional edema around calcified T. solium granulomas. There are three important findings of this study: First, seizures were relatively frequent in this closely followed population. Seizures occurred in 26.36% of the cohort and 26.67% of those with a history of seizures over the course of the study, reaching an estimated 36% incidence in 5 years of follow up. Second, perilesional edema around calcified cysticerci is very common occurring in 50% of studied patients with seizures, and third, perilesional edema is strongly associated with seizures since it was only present in 8.7% of asymptomatic controls, or 3.6% of all eligible patients at baseline.

The phenomenon of perilesional edema around calcified NCC lesions suggests a unique and specific underlying pathophysiology of seizures in this subpopulation. Because much of the injury and disease due to CC are secondary to inflammation, the most plausible hypothesis is that edema represents an inflammatory response to calcified granulomas [88].

Fujita et al. [89] suggest that perilesional edema episodes are due to the persistence of low grade inflammation driven by the presence, intermittent recognition of residual *T.* solium antigens or periodic loss of suppression of the inflammation at the calcified focus. Measures to inhibit inflammation in addition to anti-seizure treatment might be helpful in control of epilepsy due to this phenomenon. The Translocater Protein (TSPO), using Positron Emission Tomography (PET) and the selective ligand 11C-PBR28 can be a useful measure of the effectiveness of the medication.

Overall these results [83,85-89], report the better up to day characterization of mechanisms that help significantly to the understanding of the immunopathology of the NCC

Evasion strategies of the immune response by taenia solium

To survive, the parasite develops diverse immune- evasion and immune depression mechanisms: lodging in immunologically privileged sites, like eyes or brain; masking of the immune response by covering itself with host's antibodies; production of molecules that suppress or divert the immune response; and finally, processes of mutagenesis. Some of these mechanisms also include inactivation of the complement system, decrease of the number of lymphocytes, liberation of enzymes with a great lytic potential to the host's tissues and production and liberation of inflammatory response inhibitors [90]. Also, the parasite presents molecular mimicry with host's proteins, which makes the identification by the specific and innate immune system of animal hosts more difficult [51].

In NCC, more than 95% of the patients exhibit humoral response against carbohydrate - based antigens, and T. solium tegument is rich in glycoconjugates (GCs). This tegument consists in a sincytio organized in two areas: an anucleate area named distal cytoplasm, and another nucleate area known as proximal cytoplasm. By means of GCs differential labelling, in which hydrazides and lectins were labelled with fluorochromes, it was established that either fast or persistent liberation of tegumental GCs play a key role in the parasite immunomodulation, including the immune evasion and the long - term evolution with inflammatory consequences, which were observed in patients with NCC. The external surface of the parasite reacts to the host environmental changes. Moreover, high antigenicity of T. solium GCs can play a role in hypersensitivity responses, and as a last resort, in the disease symptoms [12,91-94].

Diagnosis

Serological diagnosis

The diagnosis of NCC is based upon clinical features, epidemiologic aspects, neuroimaging studies, laboratory analysis of the CSF and antibody detection in the serum [44]. Antigens used with diagnostic purposes include T. solium and T. crassiceps extracts, preparations or fractions. From them, vesicular fluid, external membrane or total extracts are taken. They show a good sensitivity, but a low specificity (especially from the total extracts), because of occurrence of cross reactions and thereby generate false positive results (because they are complex mixtures of highly conserved antigenic epitopes) with other etiological agents of various diseases. Similarly, false negative results may be observed with the serological diagnosis which limits its application because of the unreliability of the results [95,96]. It is suggested to include at least two serological tests, as a criterion to establish the NCC diagnosis [97] the use of ELISA as a screening criterion, and western blot as a confirmatory test [98,99].

A western blot assay approved by WHO and the Pan American Health Organization (PAHO) uses as antigens a partially purified antigenic preparation of glycoproteins (50, 39-42, 24, 21, 18, 14 and 13 kDa) obtained by means of lectins (Lectil - lectins) affinity chromatography designated as LLGP-EITB, from T. solium cysticerci. This assay exhibits a sensitivity of 98% and a specificity of 100% in patients with two o more viable brain lesions as demonstrated by neuroimaging studies [100].

Elliot et al. [101] demonstrated that there was no significant difference in seropositivity to T. solium by LLGP-EITB between those individuals with epilepsy (5%) and controls (4.9%) in the Momo subdivision of Ngie, Cameroon. The detection of antibodies against T. solium by LLGP-EITB in blood samples reflects a history of contact with the parasite rather than a real infection by metacestodes of T. solium. However, one of the major limitations of this study was the inability to define focal epilepsy using Electroencephalography (EEG) given the absence of this resource in rural Cameroon. It is notoriously difficult to select out focal epilepsy based upon seizure semiology alone in patients with a history of generalized epilepsy because of the secondarily generalized epilepsy.

Antigens prepared from T. crassiceps, instead of T. solium, are used in several assays: ELISA with a sensitivity and specificity of 99%, western blot with a reliability of 96%, and complement fixation reaction with a specificity and sensitivity of 93%. The use of antigens taken from T. crassiceps is favourable because they are easily obtained from BALB/c mice at the laboratory and there is no risk of human infection. On the other hand, a great number of shared antigens from both Taenia species cysticerci almost identical are observed [97-99].

Recombinant antigens and synthetic peptides

The development and implementation of molecular biology tools have allowed the production of fusion proteins in T. solium. One of the systems with efficent performance has been the coupling of proteins and peptides to the Glutathione-S-Transferase (GST) from Schistosoma japonicum, designated as NC-3 and NC-9, with a potential use in the NCC diagnosis. Starting from an ADNc expression library taken from the lambda ZAP II vector, and using serum probings from people with a clinical and serological NCC diagnosis, cloning, sequencing, and expressing these proteins was attained, and then they were purified by affinity chromatography to glutathione. A well characterized battery of serum samples was examined by ELISA, and NC-3 antigen; a sensitivity of 96.3% and a specificity of 91.5% were observed. However, a low sensitivity of 33.3% was noted for NC-9 antigen [102].

Sako et al. [103,104] obtained new T. solium fusion proteins to thioredoxin and to hexa-histidine tag or "his tag", denominated as Ag1, Ag1V1, Ag2, Ag2V1 (AG2V1 could not be expressed in heterologous expression system). Likewise, the chimeric protein Ag1V1 / Ag2 could be expressed exhibiting 100% specificity and 89.7% sensibility by ELISA. The four obtained clones showed a 53 - 94% similarity at the amino-acid level, with a hydrophobic region (import signal sequence), which indicates that it probably deals with secretory proteins located in the cysticercus' vesicular fluid. Some of these proteins have cysteine residues involved in the linking disulphide bonds, indispensable for conformational structures needed for the proteins recognition by the antibodies. That is to say, it deals with conformational epitopes, according to the results obtained under native conditions (ELISA) or under denaturing conditions (immunoblot). Another important point discussed by these authors, is the risk that implies using a heterologous expression system, because antigen's sensitivity could be lost, as occurred with Ag1 protein. According to the sequence analysis, three N- glycolisation sites were identified at the 22, 59, and 82 positions. As E. coli does not carry out post - translational modifications of the N-glycolisation type, reactivities of the sera from patients with NCC were very low by ELISA. This is partially due to the lack of carbohydrates in the antigen structure; or, according to Sako et al. [103], due to the presence of conformational epitopes in the structure of Ag1 (immunoblot - obtained results). As Ag1V1 and Ag2 are the best choices as potential diagnostic antigens, PCR technique was used to design a chimera (Ag1V1 / Ag2 hybrid) which is an antigen useful for the diagnosis of NCC by ELISA and western blot.

By chemical synthesis, nine peptides that belong to a low molecular mass (8 kDa) antigen family and have several cysteine residues in their structure were obtained. Hancock et al. [104], to standardize ELISA for the diagnosis of NCC, noted that an antigen designated as TsRS1 was 100% sensitive and 100% specific against an evaluated battery of serum samples. Whereas, Ts18 var 1 and Ts18 var 3 exhibited a sensitivity of 97% and a specificity of 100% by ELISA. With the goal of avoiding false negative results, due to the problems that depend on strains or single parasites, these authors recommend to include a group of even four recombinant or synthetic antigens to be able to establish a reliable diagnosis of NCC by ELISA.

In three Venezuelan endemic regions, five synthetic peptides (HP6-3, Ts45W-1, Ts45W-5, Ts45S-10 and TEG-1) derived from T. saginata oncosphere molecules were evaluated for the serological diagnosis of CC and NCC caused by T. solium. The positivity showed was not connected to active infection. Therefore, assays with these peptides will be potentially used only for epidemiological studies and those to determine the population exposure to the parasite [41].

The use of proteomics tools have been used to obtain recombinant antigens for diagnosis of NCC. Soluble proteins from *T. solium* cysticerci were separated by two-dimensional electrophoresis and blotted onto nitrocellulose membranes. Subtracted hybridization was performed with serum samples obtained from patients with NCC and from a NCC - negative control group. Six antigenic proteins were identified and sequenced by liquid chromatography - mass spectrometry [105]. Tsol-p27 was previously identified as a diagnostic candidate in a study conducted in Nicaragua, Central America [106]. Nhancupe et al. [105] evaluated Tsol-p27 and the antigen cC1 as potential recombinant diagnostic reagents, and also investigated the localization and partial function of Tsol-p27. Immunoblotting demonstrated that Tsol-p27 was recognized by all 10 serum samples from NCC-positive individuals, whereas cC1 was identified by only five of the 10 positive sera. None of the antigens were recognized by negative control sera. Despite the limited number of serum samples evaluated in this study, the results suggest that Tsol-p27 can be a suitable candidate for diagnosis of human NCC.

The Tsol-p27 amino acid sequence was found to be homologous to the sequences of three immunogenic proteins: P-29 of *Echinococcus granulosus*, as previously described [106]; antigen 6 of *E. multilocularis* (Genbank accession No. AAB61984); antigen 5 of *E. granulosus* (Genbank accession No. ADG37650). Protein family analysis indicated that Tsol-p27 is homologous to a group of molecules, cd07594, that include a bin / amphiphysin / rvs (BAR) domain of endophilin - B. The endophilin-B proteins are found in at least 11 different eukaryotic organisms, and they are involved in regulation of intracellular transport, lipid binding, and curvature sensing modules. Given the homology between Tsol-p27 and the *E. granulosus* protein P-29, there will most likely be cross-reactivity between those two proteins in patients who are infected with both *T. solium* and *E. granulosus.* However, since the clinical manifestations of NCC and echinococcosis differ, it should not be difficult to distinguish between the two diseases in order to make a correct diagnosis [105].

Just for educational purposes, the authors of this study estimated the sensitivity and specificity values of the antigen cC1 by immunoblot, despite the limited number of samples used: 10 derived from patients with NCC, 10 clinically healthy individuals [105]. In Table 1, some of the recombinant antigens or synthetic peptides used as diagnostic markers of CC and NCC by ELISA or western blot are summarized.

Number of access to Gen Bank	Antigen	Sensitivity (%)	Specificity (%)	Reference
X95983	HP6	85	86.6	41

AJ430567	Ts45W	85	98.6	41
AJ430566	Ts45S	85	93	41
X97000	TEG	81	81	41
AJO12669	NC-3	96.3	91.5	102
AJ012670	NC-9	33.3	85.6	102
AF356341	TsRS1	100	100	104
AF350070	Ts18 var 1	97	100	104
AF098075	Ts18 var 3	97	100	104
AF082828	Ts18	91	100	104
AF356335	Ts14	84	100	104
AF356331	Ts18 var 4	84	100	104
AF356345	Ts18 var 8	76	100	104
AF356343	TsRS2 var 1	73	100	104
AAD34598.1/*T. solium*	cC1	50	100	105
AEF14021.1/*T. solium*	Tsolp-27	76.4	95.6	107
Q7YZT0/*T. solium*	TsolHSP36	61.9	86.1	107

Table 1: Recombinant Antigens and Synthetic Peptides Used In the Diagnosis of Cysticercosis and Neurocysticercosis

Treatment

In the last 25 years, generating or favoring reduction of the number or volume of cystic and granulomatous lesions, has been attributed to cystocidal drugs (praziquantel and albendazole) generally associated to corticosteroids. As NCC is a pleomorphic disease, to establish a unique treatment pattern for all the patients is not possible. The general patient status (nourishment, immunologic condition), number, and location of the parasites are determining factors for the chemotherapeutic management [5].

Toxicological and pharmacokinetic studies carried out on humans with cystocidal agents have highlighted their fast absorption, and often little side - effects. Cystocidal therapy efficacy is followed by the reduction of the number and size of the cysticerci and correction of the ventricular dilation, observed through CT scans, and Magnetic Resonance Imaging (MRI), and by clinical evaluation, that conduces to the elimination of the corticosteroids or anticonvulsants. The risk of relevant side effects in patients as a response to cystocidal drugs is probably related to the total number, size, and location of the parasites in the CNS, as well as to the degree of inflammatory response. Surgical treatment is indicated for lesions causing progressive neurological damage, ICH or HC. The most frequent surgical intervention consists in locating a ventricular derivation to divert CSF up to the peritoneal cavity in order to control the HC. Single intraventricular cysticerci can be surgically removed, with the help of endoscopic aspiration [2,5,58,107-113].

Parenchymatous NCC

Patients with calcifications must not receive cystocidal therapy. When these appear along with convulsive crisis, the administration of antiepileptic drugs is necessary. Optimum duration of the treatment is not defined, since diverse studies have shown several relapses after suspending the drugs; even when these have controlled crisis for two years or more [6,17,108,114].

Patients with viable cysts must receive cystocidal therapy. Most of the randomized studies (some of them with double - blind design), that evaluate the effectiveness of praziquantel and albendazole against placebos, have demonstrated that these drugs are useful for both patients with hypercaptant annular lesions and those with cystic lesions. After 15 days of treatment, praziquantel produces the extinction of 60%-70% of parenchymatous cysticerci. Albendazole destroys 80% of the parenchymatous cysts, and it has shown through diverse comparative studies to be superior to praziquantel, for its higher cysts destroying percentage. Besides, it has a lower cost [6,115-119].

Patients with cysticercotic encephalitis must not receive cystocidal therapy, because it could exacerbate cerebral edemas, and increase the intracranial pressure. Patients with HC and parenchymatous cysts can receive cystocidal drugs, once the HC has been solved [6,120].

Subarachnoid NCC

Small subarachnoid and parenchymatous cysts located at the bottom of the cortical sulci must receive cystocidal treatment. Patients with HC secondary to cysticercotic arachnoiditis must be subjected to a shunt system insertion. However, a drawback regarding these cases is the highly frequency of valvular dysfunction, which is responsible for the high mortality rate registered in this disease form. In these cases, long - term administration of prednisone reduces the risk of valvular dysfunction [6,108,121].

The racemose cysticerci

This presentation is a large parasite structure composed of a conglomerate of size varying vesicles without scolices are present only in the basal subarachnoid space (BSS) or in the ventricular system; probably, because they have here room to grow in, while in the parenchyma or in other tissues the pressure prevents their development [68]. In meningeal - racemose forms, a consensus about the treatment with repeated cystocidal and corticosteroid drugs seems to exist. Nevertheless, some authors do not agree. Some works have shown a reduction of the cysts size or the meningitic process. Other groups have evaluated prolonged therapies with cystocidal drugs and corticosteroids even for months [108,122].

Del Brutto et al. [122] treated four patients, who had giant subarachnoid cysticerci, with albendazole at daily doses of 15 mg/kg of body weight for 8 days. A marked clinical improvement in every case was noted and CT studies showed that all cysts disappeared 3 months after treatment. These results evidence clinical and parasitological cure of the racemose form of NCC.

Intraventricular NCC

Depending on their size and location, ventricular cysticerci can be surgically treated or resected by direct excision or endoscopic aspiration. As the cyst could migrate within the ventricular cavities during the time between the diagnosis and the surgery, neuroimaging studies should be carried out immediately before the surgery in order to confirm its location [6,109].

Spinal cysticercosis

Cysts located in the spinal cord parenchyma are usually surgically resected to confirm the diagnosis. Isolated cases of intermedullary cysts successfully treated with albendazole and dexamethasone have been published. Leptomeningeal cysts can also be surgically resected, especially when they appear isolated or when they are grouped into a sole spinal cord. These cystocidal drugs have not been experimented on these kinds of lesions [6,123].

Searching of new drugs

Searching new chemotherapeutic targets for the treatment of NCC and other types of CC, should be based on exploiting structural differences between enzymes involved in T. solium intermediary metabolism and those of the vertebrate host. Thus, a drug must meet a series of characteristics: to produce a non - competitive inhibition, to be effective against all the parasite's evolutive stages (especially against T. solium cysticerci), to produce a radical parasitologic cure (cystocidal effect), to be effective against the whole NCC clinical spectrum, to be orally given, to go through the hematoencephalic barrier, to be efficient at low concentrations, to be well - tolerated by the patients. Up till now, albendazole and praziquantel keep on being the best choices for NCC and CC theraphy, taking into account the experience of the practitioner in the disease management and monitoring, the clinical presentation and the current consensus guidelines [6,109,114].

Development of a Vaccine

One of the alternatives to control taeniosis and cysticercosis caused by T. solium is pig vaccination. Several studies on mice, cattles, and sheeps demonstrate that it is possible to gain protection against cysticercosis by means of vaccination [124-126]. An approximation to obtain vaccines against cysticercosis consisted in testing total extracts from different Taenia species, such as, T. crassiceps [127].

Among the antigens used with vaccination purposes, those obtained from oncospheres present advantages in terms of protection percentages, unlike those antigens derived from cysticerci or cestodes. Likewise, oncosphere derived antigens used as vaccines against porcine cysticercosis, show an effectiveness, irrespective from the geographical area, as demonstrated for four independent studies from Mexico, Peru, and Cameroon, by using the same antigens, Quil A adjuvants, doses, immunization patterns, and orally given challenge assays with T. solium eggs [128-132]. One of the major advantages derived from these trials is the possibility to obtain a universal vaccine able to confer protection, no matter the different types of strains found in Africa and Latin America, where this disease is still a serious public health problem [130-134].

The use of recombinant antigens with vaccinating purposes has allowed characterizing potential targets in different species of Taenia solium, T. crassiceps, and T. ovis which exhibit variable levels of protection against porcine cysticercosis [73,132-138].

In 1999, Toledo et al. [139], a group of Mexican researchers, designed peptides based on KETc7 recombinant antigen, which is a polypeptide rich in proline amino - acid, obtaining three linear peptides denominated as GK-1, GK-2 y GK-3; among them, only GK-1 induced sterile protection (total parasite elimination) against T. crassiceps in 40 to 70% of male BALB/c mice. This 18- amino- acid peptide contains at least a B - cell epitope. Anti-GK1 antibodies recognize epitopes found in all the parasite's evolutive stages: egg, cysticercus, and adult parasite. Cytokine response against this peptide showed a Th1 / Th2 balance with both levels of INF-γ and IL-4.

Toledo et al. [139,140], based on chemical synthesis, obtain the complete sequence of linear amino - acids of the KETc1 and KETc2 antigens, and a protection of 52.7 to 100% was shown in the murine model of NCC. Analysis of the sequences and experimental data, obtained through immunofluorescence evinced B - cell and T - cell epitopes. As a consecuence of the immune response against all the parasite's evolutive stages, these authors conclude that GK1, KETc1 and KETc2 are good candidates to be a vaccine against NCC. Nevertheless, the conformation of these chemical peptides is one of its drawbacks, because it directly attempts against immunogenicity. There is the need of including haptens (GK2 and GK3), and proteolytic degradation susceptibility [139,141].

One of the great advances in the field of swine cysticercosis vaccine development was achieved in 2004; whith the use of the recombinant antigens denominated TSOL18 and TSOL45-1A, derived from oncospheres and fused to GTS. By means of glutathione affinity chematography, Flisser et al., [131] reported that these two proteins were purified and immunized pigs, reaching almost a total protection level (99.5%) by using TSOL18 as antigen. Until today, this protection level remains as the highest ever obtained against a challenge of 5,000 - 40,000 T. solium eggs in pigs. These findings and other obtained by using oncosphere derived antigens, suggested that a vaccine candidate to be tested on humans could be expected in a short term [130,142,143].

New targets

Similarly to bacteria, protozoans and helminths such as Fasciola hepatica and S. mansoni, T. solium can interact with proteins of the

fibrinolytic system, such as plasminogen and plasmin. This can happen because the parasite whether uses host's proteins to invade tissues or takes them to avoid being recognized by the immune system. Characterization of receptors that join plasminogen / plasmin in Taenia sp. offers a potential vaccine target, which has not been validated for cysticercosis yet. Similar works are being developed in malaria [144] and leishmaniosis [145].

T. solium calreticulin has been cloned; it is a protein located in tegumental and subtegumental level and is involved in the embryogenesis, ovogenesis and spermiogenesis processes. Since it represents a clue function for this cestode, it could be an excellent candidate for taeniosis vaccine [146,147]. Recombinant functional T. solium calreticulin (rTsCRT) confers differents degress of protection in the experimental model of intestinal taeniosis in hamsters [148]. The citokine response in the intestinal mucosa of hamsters infected with T. solium suggest that tapeworms induce a mixed Th1 / Th2 response (INF-γ, IL-13, IL-4) by in situ hibridization in intestinal biopsies, with a polarization toward Th2 at 2 weeks post infection, which may influence the expulsion of worms [149]. In BALB/c mice, the oral inmunization with rTsCRT, elicited high fecal IgA and the production of IL-4 and IL-5 by mesenteric lymph node cells after in vitro stimulation with rTsCRT, indicating a Th2 response, a common characteristic of protective immunity against helmints and, consequently, a desirable hallmark in the search for a human taeniosis vaccine [150].

The fatty acids bindings proteins (FABP) identified in Taenia solium (TsFABP1), could be a target to develop vaccines against CC / NCC. Protection assays carried out in a murine model of CC showed that subcutaneous immunization with TsFABP1 resulted in about 45% reduction of parasite load against an intraperitoneal challenge with T. crassiceps cysts. This reduction in parasite load correlated with the level of cellular and humoral immune responses against TsFABP1, as determined in spleen lymphocyte proliferation and ELISA testing [151]. Similar works have been performed in S. mansoni [152].

Conclusions

The human NCC should be considered as a "complex disease". Seizures are widely reported to be the most common symptoms, occurring in 70 - 90% of patients, while NCC is considered to be the main cause of late - onset epilepsy in endemic areas. The immune inflamation depends of host´s factors, the number of parasites, and also the role of innate and specific responses against antigens cysticerci. This process involves mast cells, Tregs, pro-inflamatories and anti-inflamatories cytokines, in both peripheral and CNS, and low levels of A4 and DHEA in male and females. The diagnosis of NCC is based upon neuroimaging studies (CT, MRI), laboratory analysis of the CSF, antibody detection in the serum, and epidemiological and clinical features. In terms of serological diagnosis, the lectil-lentins affinity chromatography (LLPG) is approved by WHO and PAHO. Albendazole and praziquantel are the drugs most commonly used for the treatment; however, by obtaining the nuclear genomic sequence of T. solium [153], new drugs may be obtained for the pourpose of prevention, cure, and immunotherapy. Results of protection assays with the use as vaccine rTsCRT infer that could be a candidate for use in humans.

Acknowledgements

This paper was achieved with the sponsorship of the Fondo Nacional de Ciencia, Tecnología e Innovación FONACIT (National Fund for Science, Technology and Innovation), within the Misión Ciencia framework

References

1. Davis LE, Kornfeld M (1991) Neurocysticercosis: neurologic, pathogenic, diagnostic and therapeutic aspects. Eur Neurol 31: 229-240.
2. Del Brutto OH (1997) Neurocysticercosis. Curr Opin Neurol 10: 268-272.
3. Flisser A (1998) Larval cestodes. In: L. Collier, A. Balows, and M. Sussman (edn), Topley and Wilson's microbiology and microbial infections. Arnold, London, United Kingdom.
4. del Brutto OH (1999) [Neurocysticercosis]. Rev Neurol 29: 456-466.
5. White AC Jr (2000) Neurocysticercosis: updates on epidemiology, pathogenesis, diagnosis, and management. Annu Rev Med 51: 187-206.
6. Del Brutto OH (2005) [Neurocysticercosis: up-dating in diagnosis and treatment]. Neurologia 20: 412-418.
7. Meza NW, Rossi NE, Galeazzi TN, Sánchez NM, Colmenares FI, et al. (2005) Cysticercosis in chronic psychiatric inpatients from a Venezuelan community. Am J Trop Med Hyg 73: 504-509.
8. Mafojane NA, Appleton CC, Krecek RC, Michael LM, Willingham AL 3rd (2003) The current status of neurocysticercosis in Eastern and Southern Africa. Acta Trop 87: 25-33.
9. Román G, Sotelo J, Del Brutto O, Flisser A, Dumas M, et al. (2000) A proposal to declare neurocysticercosis an international reportable disease. Bull World Health Organ 78: 399-406.
10. Ferrer E, Cortez MM, Perez H, De la Rosa M, de Noya BA, et al. (2002) Serological evidence for recent exposure to Taenia solium in Venezuelan Amerindians. Am J Trop Med Hyg 66: 170-174.
11. Ferrer E, Cabrera Z, Rojas G, Lares M, Vera A, et al. (2003) Evidence for high seroprevalence of Taenia solium cysticercosis in individuals from three rural communities in Venezuela. Trans R Soc Trop Med Hyg 97: 522-526.
12. White AC Jr (1997) Neurocysticercosis: a major cause of neurological disease worldwide. Clin Infect Dis 24: 101-113.
13. Bern C, Garcia HH, Evans C, Gonzalez AE, Verastegui M, et al. (1999) Magnitude of the disease burden from neurocysticercosis in a developing country. Clin Infect Dis 29: 1203-1209.
14. Garcia HH, Gilman R, Martinez M, Tsang VC, Pilcher JB, et al. (1993) Cysticercosis as a major cause of epilepsy in Peru. The Cysticercosis Working Group in Peru (CWG) Lancet 341: 197-200.
15. García HH, Gonzalez AE, Evans CA, Gilman RH; Cysticercosis Working Group in Peru (2003) Taenia solium cysticercosis. Lancet 362: 547-556.
16. Andriantsimahavandy A, Lesbordes JL, Rasoaharimalala B, Peghini M, Rabarijaona L, et al. (1997) Neurocysticercosis: a major aetiological factor of late-onset epilepsy in Madagascar. Trop Med Int Health 2: 741-746.
17. Nash TE, Del Brutto OH, Butman JA, Corona T, Delgado-Escueta A, et al. (2004) Calcific neurocysticercosis and epileptogenesis. Neurology 62: 1934-1938.
18. Agapejev S (2003) [Clinical and epidemiological aspects of neurocysticercosis in Brazil: a critical approach]. Arq Neuropsiquiatr 61: 822-828.
19. Garcia HH, Gonzalez AE, Rodriguez S, Gonzalvez G, Llanos-Zavalaga F, et al. (2010) [Epidemiology and control of cysticercosis in Peru]. Rev Peru Med Exp Salud Publica 27: 592-597.
20. Agudelo Florez P, Palacio LG (2003) [Prevalence of Taenia solium antibodies in humans and in pigs in an endemic area of Colombia]. Rev Neurol 36: 706-709.
21. Chacín-Bonilla L (1976) Prevalencia de Entamoeba histolytica, Entamoeba hartmanni y otros parásitos intestinales en niños hospitalizados. Invest Clin 17: 25-41.

22. Chacín de Bonilla L (1990) [The problem of intestinal parasitosis in Venezuela]. Invest Clin 31: 1-2.
23. Chacín-Bonilla L, Dikdan Y, Guanipa N, Villalobos R (1990) [Prevalence of Entamoeba histolytica and other intestinal parasites in a neighborhood of the Mara Municipality, Zulia State, Venezuela]. Invest Clin 31: 3-15.
24. Chacín-Bonilla L (1985) Geohelmintiasis en Venezuela: Un grave problema que tiende a persistir. Invest Clin 26: 1-3.
25. Chacín-Bonilla L, Dikdan Y (1981) Prevalencia de Entamoeba histolytica y otros parásitos intestinales en una comunidad suburbana de Maracaibo. Invest Clin 22: 185-203.
26. Chacin Bonilla L, Chacin-Martinez E, Espinoza E, Cardenas B (1982) A seroepidemiological study of amebiasis in children of low socioeconomic level in Maracaibo, Venezuela. Am J Trop Med Hyg 31: 1103-1106.
27. Chacín-Bonilla L, Rubio F, Cuamo Y, Añez S (1984) Prevalencia de Entamoeba histolytica y otros parásitos intestinales en una comunidad del distrito Urdaneta, estado Zulia. Invest Clin 25: 11-24.
28. Chacín-Bonilla L, Zea A, Sánchez Y, Fuenmayor N (1987) Prevalencia de Entamoeba histolytica y otros parásitos intestinales en una comunidad del distrito Miranda, estado Zulia. Invest Clin 28: 117-131.
29. Chacin-Bonilla L, Bonilla E, Parra AM, Estevez J, Morales LM, et al. (1992) Prevalence of Entamoeba histolytica and other intestinal parasites in a community from Maracaibo, Venezuela. Ann Trop Med Parasitol 86: 373-380.
30. Chacin-Bonilla L, Mejia De Young M, Cano G, Guanipa N, Estevez J, et al. (1993) Cryptosporidium infections in a suburban community in Maracaibo, Venezuela. Am J Trop Med Hyg 49: 63-67.
31. Chacín-Bonilla L, Guanipa N, Cano G, Parra AM, Estévez J, et al. (1998) Epidemiological study of intestinal parasitic infections in a rural area from Zulia State, Venezuela. Interciencia 23: 241-247.
32. Chacín-Bonilla L, Sánchez-Chávez Y (2000) Intestinal parasitic infections, with a special emphasis on cryptosporidiosis, in Amerindians from western Venezuela. Am J Trop Med Hyg 62: 347-352.
33. Goodman KA, Ballagh SA, Carpio A (1999) Case-control study of seropositivity for cysticercosis in Cuenca, Ecuador. Am J Trop Med Hyg 60: 70-74.
34. Alarcón TA, Del Brutto OH (2012) Neurocysticercosis: declining incidence among patients admitted to a large public hospital in Guayaquil, Ecuador. Pathog Glob Health 106: 310-311.
35. Hernández-Cossio O, Hernández-Fustes OJ (1999) [Neurocysticercosis and epilepsy in Cuba]. Rev Neurol 29: 1003-1006.
36. García-Pedroza F (1997) The epidemiology of neurocysticercosis in children in Mexico. In: San Esteban JE, Flisser A, González-Astiazarán A, (edn), Neurocysticercosis in chilhood. Mexico, Universidad Nacional Autónoma de México and Grupo Editorial Miguel Angel Porrúa.
37. Fleury A, Gomez T, Alvarez I, Meza D, Huerta M, et al. (2003) High prevalence of calcified silent neurocysticercosis in a rural village of Mexico. Neuroepidemiology 22: 139-145.
38. Fleury A, Morales J, Bobes RJ, Dumas M, Yánez O, et al. (2006) An epidemiological study of familial neurocysticercosis in an endemic Mexican community. Trans R Soc Trop Med Hyg 100: 551-558.
39. Schantz PM, Cruz M, Sarti E, Pawlowski Z (1993) Potential eradicability of taeniasis and cysticercosis. Bull Pan Am Health Organ 27: 397-403.
40. Schantz PM, Tsang VC (2003) The US Centers for Disease Control and Prevention (CDC) and research and control of cysticercosis. Acta Trop 87: 161-163.
41. Ferrer E, Cortéz MM, Cabrera Z, Rojas G, Dávila I, et al. (2005) Onchospheral peptide-based ELISAs as potential seroepidemiological tools for Taenia solium cysticercosis / neurocysticercosis in Venezuela. Trans Roy Soc Trop Med Hyg 99: 568-576.
42. Flisser A, Correa D (2010) Neurocysticercosis may no longer be a public health problem in Mexico. PLoS Negl Trop Dis 4: e831.
43. Flisser A, Gyorkos TW (2007) Contribution of immunodiagnostic tests to epidemiological/intervention studies of cysticercosis/taeniosis in Mexico. Parasite Immunol 29: 637-649.
44. Takayanagui OM, Odashima NS (2006) Clinical aspects of neurocysticercosis. Parasitol Int 55 Suppl: S111-115.
45. Agapejev S, Pouza AF, Bazan R, Faleiros AT (2007) [Clinical and evolutive aspects of hydrocephalus in neurocysticercosis]. Arq Neuropsiquiatr 65: 674-680.
46. das Chagas MD, D'Oliveira Júnior A, Tavares-Neto J (2003) [Clinical aspects of neurocysticercosis at semi-desert region of Brazilian northeast]. Arq Neuropsiquiatr 61: 398-402.
47. Morales NM, Agapejev S, Morales RR, Padula NA, Lima MM (2000) Clinical aspects of neurocysticercosis in children. Pediatr Neurol 22: 287-291.
48. Maldonado A, Ramos W, Pérez J, Huamán LA, Gutiérrez EL (2010) [Convulsive status epilepticus: clinico-epidemiologic characteristics and risk factors in Peru]. Neurologia 25: 478-484.
49. Kanobana K, Ruiz A, Rojas L, Andrade R, Rosado F, et al. (2013) Taenia solium cysticercosis: the case of Cuba. PLoS Negl Trop Dis 7: e2202.
50. Picado S (1968) Contribución al estudio de la neurocisticercosis en Venezuela. Invest Clin 28: 67-125.
51. Robinson P, Atmar RL, Lewis DE, White AC Jr (1997) Granuloma cytokines in murine cysticercosis. Infect Immun 65: 2925-2931.
52. Guerra-Giraldez C, Marzal M, Cangalaya C, Balboa D, Orrego MÁ, et al. (2013) Disruption of the blood-brain barrier in pigs naturally infected with Taenia solium, untreated and after anthelmintic treatment. Exp Parasitol 134: 443-446.
53. de Aluja AS, González D, Rodríguez Carbajal J, Flisser A (1989) Histological description of tomographic images of Taenia solium cysticerci in pig brains. Clin Imaging 13: 292-298.
54. de Aluja AS, Villalobos AN, Plancarte A, Rodarte LF, Hernández M, et al. (1996) Experimental Taenia solium cysticercosis in pigs: characteristics of the infection and antibody response. Vet Parasitol 61: 49-59.
55. de Aluja AS, Martinez M JJ, Villalobos AN (1998) Taenia solium cysticercosis in young pigs: age at first infection and histological characteristics. Vet Parasitol 76: 71-79.
56. de Aluja AS, Villalobos AN, Plancarte A, Rodarte LF, Hernandez M, et al. (1999) Taenia solium cysticercosis: immunity in pigs induced by primary infection. Vet Parasitol 81: 129-135.
57. Santamaría E, Plancarte A, de Aluja AS (2002) The experimental infection of pigs with different numbers of Taenia solium eggs: immune response and efficiency of establishment. J Parasitol 88: 69-73.
58. Correa D, Medina-Escutia E (1999) Host-parasite immune relationship in Taenia solium taeniosis and cysticercosis In: H.H. Garcia, and S: M. Martinez (edn) Taenia solium Taeniasis/Cysticercosis. Editorial Universo, Lima, Peru.
59. Correa MD, Plancarte A, Sandoval MA, Rodriguez-del-Rosal E, Meza-Lucas A, et al. (1989) Immunodiagnosis of human and porcine cysticercosis. Detection of antibodies and parasite products. Acta Leiden 57: 93-99.
60. Sotelo J, Del Brutto OH (2002) Review of neurocysticercosis. J Neurosurg 116: 1-7.
61. Del Brutto OH, Rajshekhar V, White AC Jr, Tsang VC, Nash TE, et al. (2001) Proposed diagnostic criteria for neurocysticercosis. Neurology 57: 177-183.
62. Flisser A (1994) Taeniasis and cysticercosis due to Taenia solium In: T. Sun. (edn), Progress in Clinical Parasitology, CRC, Boca Raton, FL, USA.
63. Sciutto E, Fragoso G, Fleury A, Laclette JP, Sotelo J, et al. (2000) Taenia solium disease in humans and pigs: An ancient parasitosis disease rooted in developing countries and emerging as a major health problem of global dimensions. Microb Infect 2: 1875-1890.
64. Proaño-Narvaez JV, Meza-Lucas A, Mata-Ruiz O, Garcia-Jeronimo R, Correa D (2002) Laboratory diagnosis of human neurocysticercosis: double blind comparison of ELISA and EITB. J Clin Microbiol 40: 2115-2118.
65. Garcia HH, Gonzalez AE, Gilman RH, Palacios LG, Jimenez I, et al. (2001) Short report: transient antibody response in Taenia solium

infection in field conditions-a major contributor to high seroprevalence. Am J Trop Med Hyg 65: 31-32.

66. Meza-Lucas A, Carmona-Miranda L, Garcia-Jeronimo RC, Torrero-Miranda A, Gonzalez-Hidalgo G, et al. (2003) Short report: limited and short-lasting humoral response in Taenia solium: seropositive households compared with patients with neurocysticercosis. Am J Trop Med Hyg 69:223-227.
67. Fleury A, Flisser A, Flores-Rivera J, Corona T (2009) Parasitic Infections. Taenia solium. In: Post-Infectious Sequelae and Long-Term Consequences of infectious Diseases. Smith JL, Brogden KA, Fratamico P. (edn), American Society for Microbiology Press.
68. Sciutto E, Cárdenas G, Adalid - Peralta L, Fragoso G, Larralde C, et al. (2013) Human neurocysticercosis: immunological features involved in the host´s susceptibility to become infected and to develop disease. Microb Infect 15: 524-530.
69. Masliniska D, Dambska M, Kaliszek A, Maslinski S (2001) Accumulation, distribution and phenotype heterogeneity of mast cells (MC) in human brains with neurocysticercosis. Folia Neuropathol 39: 7-13.
70. Hepworth MR, Danilowicz-Luebert E, Rausch S, Metz M, Klotz C, et al. (2012) Mast cells orchestrate type 2 immunity to helminths through regulation of tissue-derived cytokines. Proc Natl Acad Sci U S A 109: 6644-6649.
71. Wadia N, Desai S, Bhatt M (1988) Disseminated cysticercosis. New observations, including CT scan findings and experience with treatment by praziquantel. Brain 111 : 597-614.
72. Ostrosky-Zeichner L, García-Mendoza E, Ríos C, Sotelo J (1996) Humoral and cellular immune response within the subarachnoid space of patients with neurocysticercosis. Arch Med Res 27: 513-517.
73. Cruz-Revilla C, Rosas G, Fragoso G, López-Casillas F, Toledo A, et al. (2000) Taenia crassiceps cysticercosis: protective effect and immune response elicited by DNA immunization. J Parasitol 86: 67-74.
74. Medina-Escutia E, Morales-López Z, Proaño JV, Vazquez J, Bermúdez V, et al. (2001) Cellular immune response and Th1/Th2 cytokines in human neurocysticercosis: lack of immune suppression. J Parasitol 87: 587-590.
75. Aguilar-Rebolledo F, Cedillo-Rivera R, Llaguno-Violante P, Torres-López J, Muñoz-Hernandez O, et al. (2001) Interleukin levels in cerebrospinal fluid from children with neurocysticercosis. Am J Trop Med Hyg 64: 35-40.
76. Sciutto E, Chavarria A, Fragoso G, Fleury A, Larralde C (2007) The immune response in Taenia solium cysticercosis: protection and injury. Parasite Immunol 29: 621-636.
77. Molinari JL, Meza R, Suárez B, Palacios S, Tato P, et al. (1983) Taenia solium: immunity in hogs to the Cysticercus. Exp Parasitol 55: 340-357.
78. Flisser A, Gonzalez D, Plancarte A, Ostrosky P, Montero R, et al. (1990) Praziquantel treatment of brain and muscle porcine Taenia solium cysticercosis. 2. Immunological and cytogenetic studies. Parasitol Res 76: 640-642.
79. Sasaki O, Sugaya H, Ishida K, Yoshimura K (1993) Ablation of eosinophils with anti-IL-5 antibody enhances the survival of intracranial worms of Angiostrongylus cantonensis in the mouse. Parasite Immunol 15: 349-354.
80. Evans CA, Garcia HH, Hartnell A, Gilman RH, Jose PJ, et al. (1998) Elevated concentrations of eotaxin and interleukin-5 in human neurocysticercosis. Infect Immun 66: 4522-4525.
81. Restrepo BI, Llaguno P, Sandoval MA, Enciso JA, Teale JM (1998) Analysis of immune lesions in neurocysticercosis patients: central nervous system response to helminth appears Th1-like instead of Th2. J Neuroimmunol 89: 64-72.
82. Restrepo BI, Alvarez JI, Castaño JA, Arias LF, Restrepo M, et al. (2001) Brain granulomas in neurocysticercosis patients are associated with a Th1 and Th2 profile. Infect Immun 69: 4554-4560.
83. Robinson P, Garza A, Weinstock J, Serpa JA, Goodman JC, et al. (2012) Substance P causes seizures in neurocysticercosis. PLoS Pathog 8: e1002489.
84. Honore P, Rogers SD, Schwei MJ, Salak-Johnson JL, Luger NM, et al. (2000) Murine models of inflammatory, neuropathic and cancer pain each generates a unique set of neurochemical changes in the spinal cord and sensory neurons. Neuroscience 98: 585-598.
85. Nash TE, Del Brutto OH, Butman JA, Corona T, Delgado-Escueta A, et al. (2004) Calcific neurocysticercosis and epileptogenesis. Neurology 62: 1934-1938.
86. Nash TE, Patronas NJ (1999) Edema associated with calcified lesions in neurocysticercosis. Neurology 53: 777-781.
87. Nash TE, Pretell J, Garcia HH (2001) Calcified cysticerci provoke perilesional edema and seizures. Clin Infect Dis 33: 1649-1653.
88. Nash TE, Pretell EJ, Lescano AG, Bustos JA, Gilman RH, et al. (2008) Perilesional brain oedema and seizure activity in patients with calcified neurocysticercosis: a prospective cohort and nested case-control study. Lancet Neurol 7: 1099-1105.
89. Fujita M, Mahanty S, Zoghbi SS, Ferraris Araneta MD, Hong J, et al. (2013) PET reveals inflammation around calcified Taenia solium granulomas with perilesional edema. PLoS One 8: e74052.
90. Damian RT (1987) The exploitation of host immune responses by parasites. J Parasitol 73: 3-13.
91. White AC Jr, Robinson P, Kuhn R (1997) Taenia solium cysticercosis: host-parasite interactions and the immune response. Chem Immunol 66: 209-230.
92. Dell A, Haslam SM, Morris HR, Khoo KH (1999) Immunogenic glycoconjugates implicated in parasitic nematode diseases. Biochim Biophys Acta 1455: 353-362.
93. Cardona AE, Restrepo BI, Jaramillo JM, Teale JM (1999) Development of an animal model for neurocysticercosis: immune response in the central nervous system is characterized by a predominance of gamma delta T cells. J Immunol 162: 995-1002.
94. Alvarez JI, Rivera J, Teale JM (2008) Differential release and phagocytosis of tegument glycoconjugates in neurocysticercosis: implications for immune evasion strategies. PLoS Negl Trop Dis 2: e218.
95. Greene RM, Wilkins PP, Tsang VC (1999) Diagnostic glycoproteins of Taenia solium cysts share homologous 14- and 18-kDa subunits. Mol Biochem Parasitol 99: 257-261.
96. Pinto PS, Vaz AJ, Germano PM, Nakamura PM (2000) ELISA test for the diagnosis of cysticercosis in pigs using antigens of Taenia solium and Taenia crassiceps cysticerci. Rev Inst Med Trop Sao Paulo 42: 71-79.
97. Garcia E, Ordoñez G, Sotelo J (1995) Antigens from Taenia crassiceps cysticerci used in complement fixation, enzyme-linked immunosorbent assay, and western blot (immunoblot) for diagnosis of neurocysticercosis. J Clin Microbiol 33: 3324-3325.
98. Gottstein B, Zini D, Schantz PM (1987) Species-specific immunodiagnosis of Taenia solium cysticercosis by ELISA and immunoblotting. Trop Med Parasitol 38: 299-303.
99. Bueno EC, Snege M, Vaz AJ, Leser PG (2001) Serodiagnosis of human cysticercosis by using antigens from vesicular fluid of Taenia crassiceps cysticerci. Clin Diagn Lab Immunol 8: 1140-1144.
100. Tsang VC, Brand JA, Boyer AE (1989) An enzyme-linked immunoelectrotransfer blot assay and glycoprotein antigens for diagnosing human cysticercosis (Taenia solium). J Infect Dis 159: 50-59.
101. Elliott I, Jerome A, Angwafor SA, Smith ML, Takougang I, et al. (2013) Epilepsy and cysticercosis in Northwest Cameroon: a serological study. Seizure 22: 283-286.
102. Hubert K, Andriantsimahavandy A, Michault A, Frosch M, Mühlschlegel FA (1999) Serological diagnosis of human cysticercosis by use of recombinant antigens from Taenia solium cysticerci. Clin Diagn Lab Immunol 6: 479-482.
103. Sako Y, Nakao M, Ikejima T, Piao XZ, Nakaya K, et al. (2000) Molecular characterization and diagnostic value of Taenia solium low-molecular-weight antigen genes. J Clin Microbiol 38: 4439-4444.
104. Hancock K, Khan A, Williams FB, Yushak ML, Pattabhi S, et al. (2003) Characterization of the 8-kilodalton antigens of Taenia solium

metacestodes and evaluation of their use in an enzyme-linked immunosorbent assay for serodiagnosis. J Clin Microbiol 41: 2577-2586.

105. Nhancupe N, Salazar-Anton F, Noormahomed EV, Afonso S, Lindh J (2013) Further characterization of Tsol-p27 as a diagnostic antigen in sub-Saharan Africa. Exp Parasitol 135: 573-579.
106. Salazar-Anton F, Lindh J (2011) Taenia solium: a two-dimensional Western blotting method combined with the use of an EST-library for the identification of immunogenic proteins recognized by sera from neurocysticercosis patients. Exp Parasitol 128: 371-376.
107. Salazar-Anton F, Tellez A, Lindh J (2012) Evaluation of an immunodot blot technique for the detection of antibodies against Taenia solium larval antigens. Parasitol Res 110: 2187-2191.
108. García HH, Evans CA, Nash TE, Takayanagui OM, White AC Jr, et al. (2002) Current consensus guidelines for treatment of neurocysticercosis. Clin Microbiol Rev 15: 747-756.
109. Garcia HH, Pretell EJ, Gilman RH, Martinez SM, Moulton LH, et al. (2004) A trial of antiparasitic treatment to reduce the rate of seizures due to cerebral cysticercosis. N Engl J Med 350: 249-258.
110. Colli BO, Valença MM, Carlotti CG, Machado HR, Assirati JA (2002) Spinal cord cysticercosis: neurosurgical aspects. Neurosurg Focus 12: e9.
111. Jung H, Cárdenas G, Sciutto E, Fleury A (2008) Medical treatment for neurocysticercosis: drugs, indications and perspectives. Curr Top Med Chem 8: 424-433.
112. Sotelo J, Del Brutto OH (2002) Review of neurocysticercosis. Neurosurg Focus 12: e1.
113. Nash TE (2003) Human case management and treatment of cysticercosis. Acta Trop 87: 61-69.
114. Del Brutto OH (1994) Prognostic factors for seizure recurrence after withdrawal of antiepileptic drugs in patients with neurocysticercosis. Neurology 44: 1706-1709.
115. Sotelo J, Escobedo F, Rodriguez-Carbajal J, Torres B, Rubio-Donnadieu F (1984) Therapy of parenchymal brain cysticercosis with praziquantel. N Engl J Med 310: 1001-1007.
116. Garcia HH, Gilman RH, Horton J, Martinez M, Herrera G, et al. (1997) Albendazole therapy for neurocysticercosis: a prospective double-blind trial comparing 7 versus 14 days of treatment. Cysticercosis Working Group in Peru. Neurology 48: 1421-1427.
117. Kalra V, Dua T, Kumar V (2003) Efficacy of albendazole and short-course dexamethasone treatment in children with 1 or 2 ring-enhancing lesions of neurocysticercosis: a randomized controlled trial. J Pediatr 143: 111-114.
118. Del Brutto OH, Campos X, Sánchez J, Mosquera A (1999) Single-day praziquantel versus 1-week albendazole for neurocysticercosis. Neurology 52: 1079-1081.
119. Pretell EJ, Garcia HH, Custodio N, Padilla C, Alvarado M, et al. (2000) Short regimen of praziquantel in the treatment of single brain enhancing lesions. Clin Neurol Neurosurg 102: 215-218.
120. Noboa C (1992) Encefalitis cisticercosa: análisis de 10 casos. Rev Ecuat Neurol 1: 61-71.
121. Suastegui Roman RA, Soto-Hernandez JL, Sotelo J (1996) Effects of prednisone on ventriculoperitoneal shunt function in hydrocephalus secondary to cysticercosis: a preliminary study. J Neurosurg 84: 629-633.
122. Del Brutto OH, Sotelo J, Aguirre R, Díaz-Calderón E, Alarcón TA (1992) Albendazole therapy for giant subarachnoid cysticerci. Arch Neurol 49: 535-538.
123. Corral I Quereda C, Moreno A, López-Vélez R, Martínez-San-Millán J, et al. (1996) Intramedullary cysticercosis cured with drug treatment. A case report. Spine (Phila Pa 1976) 21: 2284-2287.
124. Verastegui M, Gilman RH, Gonzales A, Garcia HH, Gavidia C, et al. (2002) Taenia solium oncosphere antigens induce immunity in pigs against experimental cysticercosis. Vet Parasitol 108: 49-62.
125. Flisser A, Lightowlers MW (2001) Vaccination against Taenia solium cysticercosis. Mem Inst Oswaldo Cruz 96: 353-356.
126. Gonzalez AE, Gauci CG, Barber D, Gilman RH, Tsang VC, et al. (2005) Vaccination of pigs to control human neurocysticercosis. Am J Trop Med Hyg 72: 837-839.
127. Sciutto E, Fragoso G, Trueba L, Lémus D, Montoya RM, et al. (1990) Cysticercosis vaccine: cross-protecting immunity with T. solium antigens against experimental murine T. crassiceps cysticercosis. Parasite Immunol 12: 687-696.
128. Lightowlers MW (1994) Vaccination against animal parasites. Vet Parasitol 54: 177-204.
129. Lightowlers MW, Colebrook AL, Gauci CG, Gauci SM, Kyngdon CT, et al. (2003) Vaccination against cestode parasites: anti-helminth vaccines that work and why. Vet Parasitol 115: 83-123.
130. Lightowlers MW, Flisser A, Gauci CG, Heath DD, Jensen O, et al. (2000) Vaccination against cysticercosis and hydatid disease. Parasitol Today 16: 191-196.
131. Flisser A, Gauci CG, Zoli A, Martinez-Ocaña J, Garza-Rodriguez A, et al. (2004) Induction of protection against porcine cysticercosis by vaccination with recombinant oncosphere antigens. Infect Immun 72: 5292-5297.
132. Kyngdon CT, Gauci CG, Rolfe RA, Velasquez-Guzman JC, Farfan-Salazar MJ, et al. (2006) In vitro oncosphere-killing assays to determine immunity to the larvae of Taenia pisiformis, Taenia ovis, Taenia saginata and Taenia solium. J Parasitol 92: 273-281.
133. Jabbar A, Kyngdon CT, Gauci CG, Walduck AK, McCowan C, et al. (2010) Localisation of three host-protective oncospheral antigens of Taenia ovis. Int J Parasitol 40: 579-589.
134. Jabbar A, Crawford S, Gauci CG, Walduck AK, Anderson GA, et al. (2010) Oncospheral penetration glands and secretory blebs are the sources of Taenia ovis vaccine antigens. Infect Immun 78: 4363-4373.
135. Johnson KS, Harrison GB, Lightowlers MW, O'Hoy KL, Cougle WG, et al. (1989) Vaccination against ovine cysticercosis using a defined recombinant antigen. Nature 338: 585-587.
136. González E, Robles Y, Govezensky T, Bobes RJ, Gevorkian G, et al. (2010) Isolation of neurocysticercosis-related antigens from a genomic phage display library of Taenia solium. J Biomol Screen 15: 1268-1273.
137. Harrison GB, Heath DD, Dempster RP, Gauci C, Newton SE, et al. (1996) Identification and cDNA cloning of two novel low molecular weight host-protective antigens from Taenia ovis oncospheres. Int J Parasitol 26: 195-204.
138. Lightowlers MW (1999) Eradication of Taenia solium cysticercosis: a role for vaccination of pigs. Int J Parasitol 29: 811-817.
139. Toledo A, Larralde C, Fragoso G, Gevorkian G, Manoutcharian K, et al. (1999) Towards a Taenia solium cysticercosis vaccine: an epitope shared by Taenia crassiceps and Taenia solium protects mice against experimental cysticercosis. Infec Immun 67: 2522-2530.
140. Toledo A, Fragoso G, Rosas G, Hernández M, Gevorkian G, et al. (2001) Two epitopes shared by Taenia crassiceps and Taenia solium confer protection against murine T. crassiceps cysticercosis along with a prominent T1 response. Infect Immun 69: 1766-1773.
141. Rosenthal KS, Zimmerman DH (2006) Vaccines: all things considered. Clin Vaccine Immunol 13: 821-829.
142. Plancarte A, Flisser A, Gauci CG, Lightowlers MW (1999) Vaccination against Taenia solium cysticercosis in pigs using native and recombinant oncosphere antigens. Int J Parasitol 29: 643-647.
143. Martinez-Ocana J, Romero-Valdovinos M, G de Kaminsky R, Maravilla P, Flisser A (2011) Immunolocalization of TSOL18 and TSOL45-1A, the successful protective peptides against porcine cysticercosis, in Taenia solium oncospheres. Parasit Vectors 4: 3.
144. Pal-Bhowmick I, Mehta M, Coppens I, Sharma S, Jarori GK (2007) Protective properties and surface localization of Plasmodium falciparum enolase. Infect Immun 75: 5500-5508.
145. Vanegas G, Quiñones W, Carrasco-López C, Concepción JL, Albericio F, et al. (2007) Enolase as a plasminogen binding protein in Leishmania mexicana. Parasitol Res 101: 1511-1516.

146. Mendlovic F, Ostoa-Saloma P, Solís CF, Martínez-Ocaña J, Flisser A, et al. (2004) Cloning, characterization, and functional expression of Taenia solium calreticulin. J Parasitol 90: 891-893.

147. Mendlovic F, Carrillo-Farga J, Torres J, Laclette JP, Flisser A (2006) Differential expression of calreticulin in developmental stages of Taenia solium. J Parasitol 92: 789-795.

148. León-Cabrera S, Cruz-Rivera M, Mendlovic F, Avila-Ramírez G, Carrero JC, et al. (2009) Standardization of an experimental model of human taeniosis for oral vaccination. Methods 49: 346-350.

149. Avila G, Aguilar L, Romero-Valdovinos M, Garcia-Vazquez F, Flisser A (2008) Cytokine response in the intestinal mucosa of hamsters infected with Taenia solium. Ann N Y Acad Sci 1149: 170-173.

150. Fonseca-Coronado S, Ruiz-Tovar K, Pérez-Tapia M, Mendlovic F, Flisser A (2011) Taenia solium: immune response against oral or systemic immunization with purified recombinant calreticulin in mice. Exp Parasitol 127: 313-317.

151. Illescas O, Carrero JC, Bobes RJ, Flisser A, Rosas G, et al. (2012) Molecular characterization, functional expression, tissue localization and protective potential of a Taenia solium fatty acid-binding protein. Mol Biochem Parasitol 186: 117-125.

152. Tendler M, Brito CA, Vilar MM, Serra-Freire N, Diogo CM, et al. (1996) A Schistosoma mansoni fatty acid-binding protein, Sm14, is the potential basis of a dual-purpose anti-helminth vaccine. Proc Natl Acad Sci U S A 93: 269-273.

153. Tsai IJ, Zarowiecki M, Holroyd N, Garciarrubio A, Sanchez-Flores A, et al. (2013) The genomes of four tapeworm species reveal adaptations to parasitism. Nature 496: 57-63.