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Neurocysticercosis

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Cysticercosis is an infection caused by *Taenia solium* larvae (cysticerci). When the cysticercus is lodged in the central nervous system (CNS), the disease is known as neurocysticercosis (NCC). NCC is the most frequent and most widely disseminated human neuroparasitosis. It is endemic in many parts of the world, particularly Latin America, Africa, and Asia, and still relatively frequent in Portugal, Spain and Eastern European countries. It is also endemic in developed countries with high rates of immigration from endemic areas. Man may act as an intermediate host after ingestion of mature, viable *T. solium* eggs via the fecal-oral route. The development of lesions in the brain and leptomeninges, and the consequent onset of symptoms associated with NCC are mainly due to the host immune-inflammatory response. As long as the cysticercus remains viable, there is relative host immune tolerance. It is only when the parasite dies that massive antigen exposure occurs, with intensification of the immune response/inflammatory reaction and the appearance or worsening of symptoms. NCC can be asymptomatic or cause widely varied clinical manifestations, such as seizures, increased intracranial pressure, ischemic cerebrovascular disease, dementia, and signs of compression of the spinal roots/cord. The combination of two or more symptoms is common. Such clinical polymorphism is determined by 1) the number of lesions (single or multiple cysticerci); 2) the location of CNS lesions (subarachnoid, intracerebral, intraventricular, intramedullary); 3) the type of cysticercus (*Cysticercus cellulosae, Cysticercus racemosus*); 4) the stage of development and involution of the parasite (vesicular or viable, necrotic, fibrocalcified nodule); and 5) the intensity of the host immune-inflammatory response (no inflammatory reaction, leptomeningitis, encephalitis, granular ependymitis, arteritis).

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Introduction

Cysticercosis is an infection caused by *Taenia solium* larvae following the ingestion of eggs excreted in human feces by the adult worm. Up until the second half of the 19th century, the larval form of this parasite was believed to be a distinct species, and the name *Cysticercus cellulosae* was given to it in 1809 by Rudolphi. Sanctioned by usage, such designation persisted, even after the life cycle of *T. solium* had been demonstrated. The name *Cysticercus*, proposed by Linnaeus, is derived from the Greek words *kustis* (cyst, vesicle) and *kercos* (tail), and is justified by the fact that the parasite contains a structure that is similar to a small tail. As for the term *cellulosae*, it was proposed by Rudolphi in 1809 based upon the frequent location of the cysticercus in the connective tissue.

The designation *neurocysticercosis* (NCC) refers to the presence of cysticerci in the central nervous system. NCC is the most frequent and most widely disseminated human neuroparasitosis. Even though it is a rare cause of death in autopsied adult patients - 1% in a series of 13,662 autopsies performed in Mexico City - (63) it frequently produces neurological symptoms that can affect the quality of the patient's life. In addition, NCC has a significant social-economic impact, not only due to the permanent or temporary disability it causes in individuals at productive ages, but also because of the high cost of diagnosis and treatment. In Mexico, the expenses for hospitalization, computerized tomography (CT), neurosurgery, and drugs for the 2700 new cases of NCC hospitalized in 1986 added up to US$14.5 million (31).

Epidemiology

NCC is endemic in most developed and developing countries of Latin America, Central and South Africa, and Asia (notably China, India, and Indonesia). It is still relatively frequent in Portugal, Spain, and Eastern European countries, particularly Poland and Romania (1,23,45,54,56,75,77,82). NCC is also endemic in developed countries, among social groups including emigrants, and has been in expan-

sion over the last decades. In the southwestern region of the U.S., for example, there has been a dramatic increase, starting in the mid-70's, in the number of reported cases of NCC. This corresponds to the increase in the number of Hispanic immigrants from Latin America (36,48,77). The disease particularly affects communities in which hygienic conditions are poor. Life habits within the microenvironment of the patient's household are an important factor, since one of the common forms of egg transmission is by contamination of the hands within the household (76). Other equally important factors that contribute to the maintenance of high prevalence rates of cysticercosis and NCC in endemic areas (24,76) are 1) the use of contaminated water for the irrigation of vegetables; 2) poor sanitary conditions; 3) free sale and consumption of pork infested with cysticerci from domestically bred pigs or clandestine slaughterhouses; and 4) direct personal contact with *Taenia* carriers. Besides, the problems inherent to meat inspection, in which only a small number of infested animals are identified, are well known (3).

The frequency of NCC in series of autopsied patients from general hospitals varies from 0.1 to 3.6% in several countries of Latin America, Africa, and Asia. In Mexico City, an endemic region for NCC, incidence of the disease in autopsies of adult patients did not alter significantly - between 3.2 and 3.6% - in the period 1946-1974 (63). Although series of autopsies constitute a useful method for estimating the prevalence of NCC, they are not without limitations. Few professionals with adequate skills in neuropathology are available in areas where NCC is endemic, and many of the existing studies based on autopsy findings were performed by general pathologists, with no mention being made of the technique used for brain study. In many cases, the neuropathological study consisted simply of a few non-standardized cuts across the fresh brain, with no parallel, frontal cuts being made. Also, a microscopic examination was either not performed or, when performed at all, was restricted to a few fragments collected at random. An example of such situation can be obtained from the records of the Department of Pathology and Legal Medicine of the School of Medicine of the Federal University of Minas Gerais, in Belo Horizonte, capital city of the state of Minas Gerais, in southeastern Brazil, a country where NCC is endemic. At this Department, which performs autopsies on patients from a general hospital, the frequency of NCC in 19,328 consecutive autopsies carried out in the period 1938-1976 was 0.4%, whereas in the period 1977-1996 the rate of incidence was 3.6% in 2,259 consecutive autopsies. In the latter period, if patients aged two years or less were excluded, the frequency of NCC in 1129 consecutive autopsies would be 7.3%. A reduction in the frequency of NCC was observed over the years 1987-1996 (4.9%), as compared with the previous decade (8.9%). Even though other factors could explain the difference in NCC prevalence between the two large periods indicated above, the most important one was certainly the change in the method used for brain examination. In the period 1938-1976, the non-fixed brain was, in most cases, examined during the autopsy, and the microscopic examination was either not performed or, when performed, was limited to a few fragments collected at random. During the period 1977-1996, however, a standardized technique was used for the neuropathological study, which consisted of macroscopic examination after brain fixation and microscopic analysis of fragments from the frontal, parietal, temporal and occipital lobes, basal ganglia, thalamus, midbrain, pons, medulla, and cerebellum. From the above considerations, it can be inferred that the incidence of NCC has probably been underestimated in several of the reported series of autopsies.

Life Cycle of T. Solium. The adult *T. solium* tapeworm lives in the small intestine of man, its only definitive host. It attaches itself to the intestinal mucosa by means of a scolex equipped with four lateral suckers especially adapted for adhering, and a rostellum, located in the terminal portion of the scolex, which bears 25-50 hooklets (9,57). Like most other cestodes, *T. solium* is a hermaphrodite, and the gravid proglottids containing the eggs are released in the intestinal lumen. From there they reach the environment by passive discharge in the feces. The number of proglottids (each containing 60,000 to 75,000 eggs) that break off from the adult worm per day is variable, the average being 4-5, which represents 200-400 thousand eggs per day (91). The eggs are spherical and measure 30-40 µm in diameter. After being liberated from the proglottids, the eggs can be ingested by the pig (the most common intermediate host, due to its coprophagic habits), by man, and by other mammals. Probably only a small portion of the ingested eggs escape local destruction by the host. Once in the digestive tract, the eggs lose their coat by the action of the gastric and pancreatic enzymes, which liberate hexacant embryos or oncospheres. These are provided with three pairs of hooklets and measure approximately 20 µm in diameter. Aided by their hooklets, the oncospheres cross the intestinal wall and local venules, enter the venous systemic circulation and are carried to the heart, where they enter the arterial systemic circulation to reach the definitive organ of the host (skeletal muscles, central nervous system, subcutaneous tissue, eye, etc.). Here the oncospheres lose their hooklets, acquire a vesicular shape, and evolve into cysticerci by gradual evagination of the protoscolex (invaginated scolex); their evolution takes place over a period of two months (27). It is accepted that, when lodged in the eye and cerebral ventricles, the parasite can repeatedly evaginate and invaginate, while searching for an appropriate location for attaching itself (33). This is made easier by the absence of a host-derived inflammatory

capsule around the parasite. The life cycle is completed when undercooked pork infested with viable cysticerci is eaten by human beings (82). Upon reaching the small intestine, the scolex evaginates and attaches itself to the internal mucosa, where it gradually evolves into the adult tapeworm.

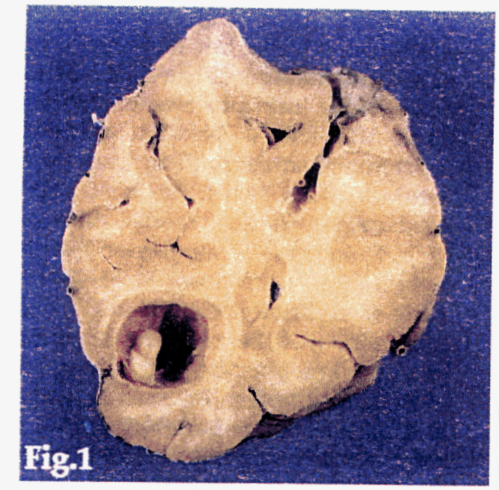
Man may act as an intermediate host by ingesting mature *T. solium* eggs via three different fecal-oral routes: 1) by heteroinfection, the most common route, in which eggs present, for example, in food contaminated by the feces of *Taenia* carriers are ingested; 2) by exogenous autoinfection, whereby a carrier of the adult *T. solium* tapeworm ingests food contaminated by eggs from the tapeworm living in his own intestine, this route being far less frequent than the former, as it is quite uncommon to find patients with both cysticercosis and taeniasis (23,56); and 3) by endogenous autoinfection, in which the eggs of the adult tapeworm living in the small intestine return to the stomach due to reverse peristalsis. This form of infection, however, is highly questionable, considering that the mature, infective eggs are contained in the terminal gravid proglottids, therefore, several meters away from the scolex, which is located in the initial third portion of the small intestine. Thus, the possibility that proglottids may return to the stomach and duodenum, where the oncospheres would be liberated by the action of the digestive enzymes, is quite remote.

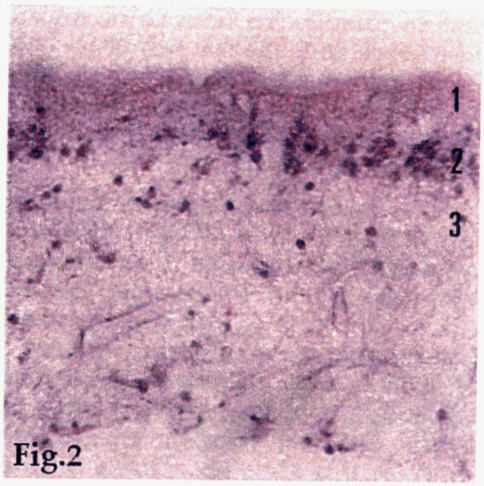
Pathogenesis

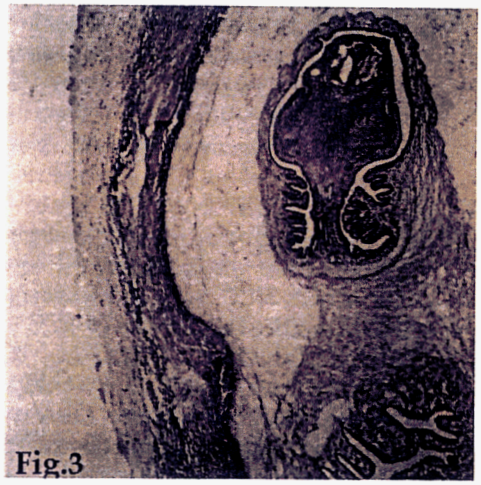
The mechanisms by which cysticercal lesions develop in the brain, spinal cord and leptomeninges depend on a combination of host immune-inflammatory response and the compressive and obstructive processes, associated or not, induced by the parasite (56,86,93). Compressive processes result from the mass effect produced by a volumous cysticercus or a large number of small cysticerci. Obstructive processes may arise from blocking cerebrospinal fluid (CSF) circulation by cysticerci lodged in the ventricles or subarachnoid space. More frequently, however, obstruction is induced by the development of granular ependymitis, in the case of ventricular NCC, and fibrosing chronic leptomeningitis, in the case of subarachnoid NCC.

The development of lesions in the nerve tissue and leptomeninges, with the consequent onset of symptoms associated with NCC, is mainly due to the host immune-inflammatory response. A cysticercus contains a large number of antigens, yet the inflammatory reaction around it is often discrete or even absent. It is not until the cysticercus dies that there is massive exposure of antigens, intensification of the immune response/inflammatory reaction, and the appearance or worsening of symptoms (16,20,30, 32,60,79,90). Little is known about the reasons for such initial immune tolerance and which antigens are responsible for intensification of the inflammatory reaction. As in other chronic infections, the parasite remains viable for many years, and during such period modulation of the host immune system may occur. (38). Immune evasion by the parasite may result from (34) 1) isolation of the more important glycoproteic antigens of the parasite within the cyst, without contact with the host; 2) binding of some host antigens to the cyst wall - molecular mimetism - (51); 3) increase of suppressor T-cells; 4) polyclonal lymphocyte-B activation; 5) antigen variation in the cases of multiple infection (6); 6) inhibition of the Clq fraction of the complement system and of both classical and alternate activation pathways of the complement system, or complement activation away from the parasite, permitting it to evade complement-mediated destruction (90); and 7) binding of the parasite to the Fc portion of the antibody, which would be used as a source of protein (90).

Some *C. cellulosae* antigens have been considered relevant in human NCC, when CSF is used as a source of primary antibody. The glycocalyx that lines the cyst wall tegument has the structure that most strongly reacted to CSF antibodies (78). Humoral immune response in NCC is mainly constituted by IgG immunoglobulins and complement (31,53). High IgG titers are found in the serum and CSF of patients with NCC. Such levels are significantly more elevated in the severe forms of NCC (presenting with increased intracranial pressure, leptomeningitis, intraventricular cysticerci, vasculitis, multiple cysticercosis, giant cysticerci), than in the milder or asymptomatic forms of the disease (few cysticerci in the leptomeninges of the cerebral convexity, intracerebral cysticerci, calcified or not, sometimes associated with seizures) (13,95). These data suggest that the inflammatory reaction is largely mediated by humoral immune response. Following treatment with praziquantel (a cysticidal drug), elevated IgC titers are observable in the CSF, but not in serum, suggesting the local production of specific antibodies (30). Therefore, humoral immune response may be relevant not only in the elimination of cysticercal antigens, but also in the genesis of nerve tissue and leptomeningeal lesions, due to inflammatory reaction produced (encephalitis and leptomeningitis). As far as cellular immune response is concerned, the studies conducted so far are few and inconclusive. When evaluated by CT, intensity of the inflammatory reaction around intracerebral cysticerci is more severe in females than in males (20). Although such difference remains unexplained, it suggests an interaction between hormonal factors and immune response modulation. It may also explain the higher prevalence of cysticercotic encephalitis in women. Studies were made on histocompatibility leukocyte antigens (HLA) in NCC that showed a direct relation between the presence of these antigens on the surface of cysticerci and microscopic signs of damage in cysticerci (14). In a comparison between a group of







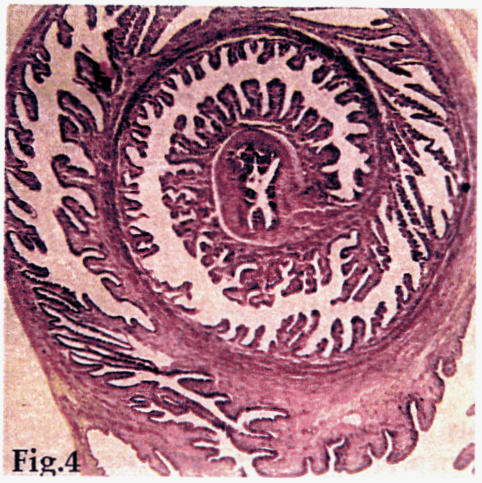


Figure 1. *C. cellulosae* in the occipital lobe. The cyst has a thin wall and contains an invaginated scolex.

Figure 2. Wall of a cysticercal cyst with cuticular (1), cellular (2) and reticular (3) layer. H&E, X450

Figure 3. *C. cellulosae*. Cyst wall surrounded by a zone of fibrosis permeated with mononuclear inflammatory infiltrate. Note scolex within the cyst. H&E., X45.

Figure 4. *C. cellulosae*. Panoramic view of spiral canal. H&E, X45.

patients with intracerebral NCC and a group of controls of the same ethnic origin (Mexican mestizo population), a considerable increase in HLA-A28 and an equally significant decrease in HLA-DQw2 were observed in the patients with NCC (21). The relative risk of an HLA-A28-positive individual developing NCC was 3.6 times higher. Thus, the major histocompatibility complex probably has a role in the susceptibility to and resistance against intracerebral NCC. The hypothesis of immunodeficiency in patients with asymptomatic NCC has been raised by some authors, based on the association between the incidence of such parasitosis, with viable cysticerci demonstrated by neuroimaging, and diseases accompanied by immunodeficiency such as leukemia, ataxia-telangiectasis, IgA deficiency and lymphoma, and HIV infection (67,85,89). According to these authors, in areas where NCC is endemic, immunodeficiency might even increase the frequency or severity of NCC. Such possibility, however, should be regarded with reserve, considering that 1) the finding of an endemic infectious disease associated with another pathology or infection is not uncommon in patients from endemic regions; 2) with the exception of these few reports, there has been no evidence of an increase in the number of cases of NCC patients that have AIDS (acquired immunodeficiency syndrome); 3) immune humoral response, apparently predominant in NCC, and the absence of an intracellular stage in the life cycle of *T. solium* make it less likely for the cysticercus to act as an opportunist agent, unlike obligatory intracellular parasites, which depend on the depletion of T-helper CD4+, such as *Toxoplasma gondii, Pneumocystis carinii,* etc., commonly found in patients with AIDS (40,46).

Pathology

C. cellulosae is the most frequently observed form

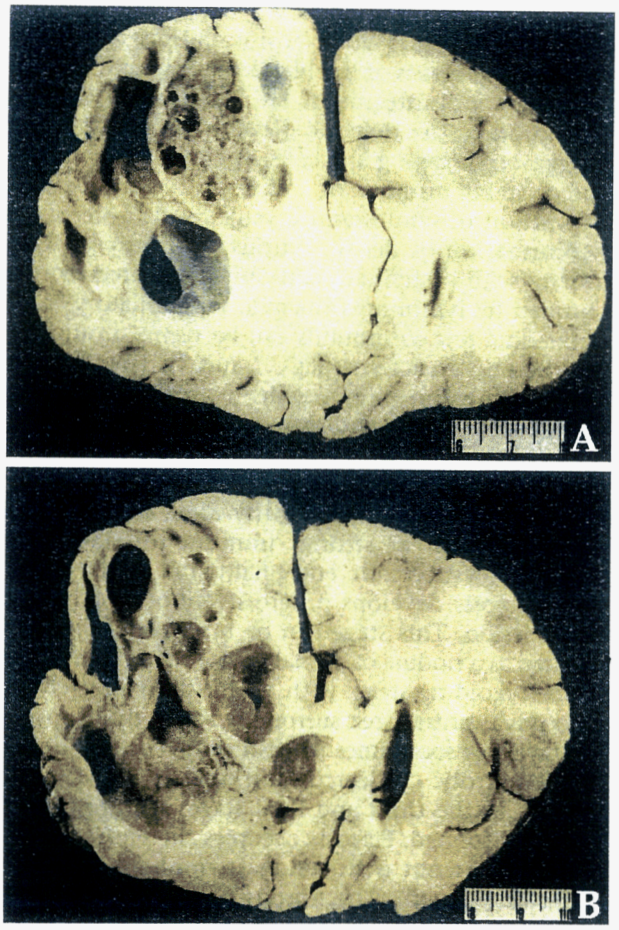


Figure 5. (A) and **(B)**. *C. racemosus* in the left frontal lobe. Note the unequal size of the cysts, the absence of a scolex, and the mass effect.

of cysticercus in NCC cases (63). It is characterized by a rounded or oval cyst measuring from 5 to 15 mm in diameter, with a thin, translucent, membranous wall (Fig. 1). The cyst is filled with a clear fluid and contains a pearly white invaginated scolex (protoscolex) (57,82). Larger cysts, 2 to 4 cm in diameter, are rarely found. Histologically, the outer portion of the cyst, the tegument, is a syncytium composed of microtriches lined with a glycocalyx. The cyst wall (Fig. 2) has three layers (9,10,27, 57,74,82): an outer or eosinophilic cuticular layer with a smooth contour, beneath which are bundles of muscle fibers; a middle or cellular layer with small, evenly distributed dark-staining nuclei; and an inner or reticular layer containing loosely arranged fibrils, excretory canaliculi, and small, oval or round calcareous corpuscles. If acid fixatives are used, the calcareous corpuscles would dissolve and only empty spaces would remain in their place. The protoscolex has a structure similar to that of the adult tapeworm. It is attached to the cyst by means of a neck and has a spiral canal (Figs. 3 and 4). Suckers and a rostellum armed with hooklets are often observed.

The larval variety known as *Cysticercus racemosus*, a designation proposed by Zenker in 1882 (from the Latin *racemus*, which means "bunch of grapes"), is less frequently found. The coexistence of *C. cellulosae* and *C. racemosus* is observed in approximately 10% of the cases of NCC (63). In the racemose form (Fig. 5), the cysts are larger (4-12 cm) than those usually seen in *C. cellulosae*, and the scolex is absent (63). This form may appear as a single cyst or, more frequently, as multiple unequally sized cysts arranged like a cluster of grapes (5,63). Although histologically similar to that of *C. cellulosae*, the cyst wall of *C. racemosus* is characteristically folded and convoluted, and the external surface of the tegument displays small, round protrusions (Fig. 6) along most of its length (5,57,63). It has been admitted that the racemose form arises from *C. cellulosae* segmentation and/or the sprouting of new cysts, with gradual expansion of each cyst and degeneration of the scolex (63). Forms representing a transition between the two types of cysticercus have been reported. That *C. racemosus* may be a variety of the *T. solium* larva is demonstrated by 1) the coexistence of *C. cellulosae* and *C. racemosus* in the same individual (63); 2) the finding of forms representing a transition between the two types of cysticerci (62); 3) the demonstration of remnants of the scolex, including hooklets (5,62). However, little is known about the causes for, or the factors that may lead to, the development of *C. racemosus*. Neither the racemose nor the intermediate forms have been found in animals other than man.

The number of parasites varies widely in NCC. In 20-53% of the cases, solitary cysticerci are found (48,63). When multiple, the cysticerci are usually in a small number; the finding of hundreds of parasites, characterizing the disseminated form, is rare (88). Cysticerci may become lodged in any part of the leptomeninges, brain and spinal cord, but there are preferred sites, depending on the larval variety. The preferred site of location of *C. cellulosae* is the subarachnoid spaces of the cerebral convexity, followed by the brain parenchyma and the ventricular cavities (63). In the brain parenchyma, the parasite is usually located in the cortex and in the zones of transition between the gray cortical and the white subcortical matter. Infection in the basal ganglia, brain stem and cerebellum is less common. Intramedullary location is rare (8,39,61). Of the ventricular cavities, the fourth ventricle and the lateral ventricles are the most frequently affected areas. *C. racemosus* has a predilection for the basal cisterns, sylvian fissure, and ventricular cavities (86). Location in the brain parenchyma is rare. The combination of multiple locations is common.

Because cysticercosis is a chronic, slow-progressing, frequently asymptomatic disease, which is only diagnosed when viable, necrotic or fibrocalcified cysticerci are identified by neuroimaging procedures or at autopsy, the early stages of development of the *T. solium* larva are not detectable in the patients. Once formed, the cysticercus may remain viable in the

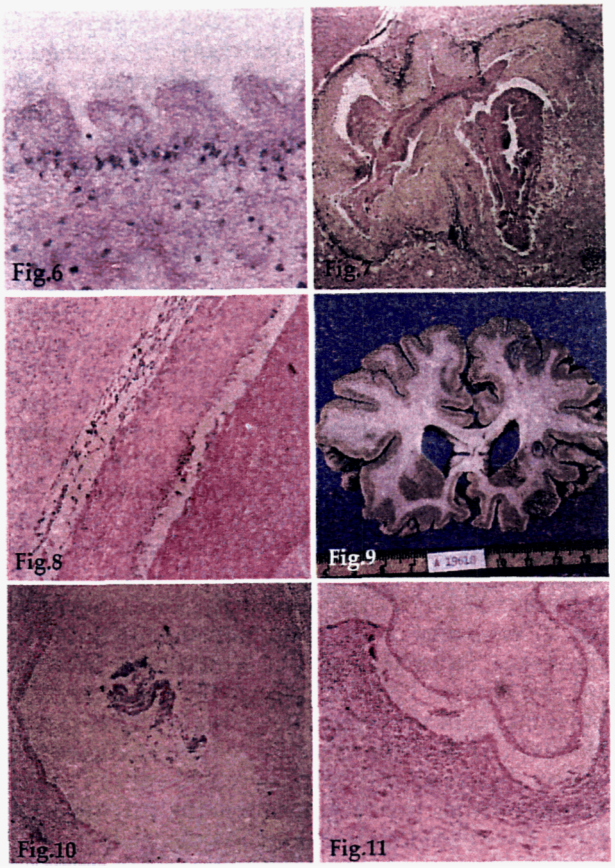


Figure 6. *C. racemosus.* Note the small protrusions on the external face of the cyst wall tegument. Compare with **Figure 2** H&E, X450.

Figure 7. Necrotic *C. cellulosae* surrounded by a thick zone of fibrosis with a partly circinate contour and, more externally, mononuclear inflammatory infiltrate. H&E, X45.

Figure 8. Necrotic *C. cellulosae.* From right to left, remnants of the larva, zone of fibrosis, mononuclear inflammatory infiltrate, and adjacent nerve tissue showing fibrillary astrocytosis.

Figure 9. Necrotic *C. cellulosae* in the right frontal lobe.

Figure 10. Fibrocalcified *C. cellulosae.* The lesion is almost entirely occupied by fibrosis with a partly circinate contour. H&E, X45.

Figure 11. *C. racemosus.* Intense inflammatory reaction and fibrillary astrocytosis around the cyst wall. A small loculus is beginning to be formed. H&E, X113.

CNS for several years (usually 1-3 years), depending, among other factors, on the greater or lesser host immune tolerance. Morphologically, three stages of development and regression of the cysticercus in the CNS are recognized (1,26,58,60,63). In the first stage, known as cystic or vesicular stage, the cysticercus is viable and composed of a well-defined, fluid-filled membrane which, unlike hydatid cysts, contains only one scolex. Discrete to moderate lymphoplasmacytic inflammatory infiltrate and a few eosinophils may or not be present around the cysticercus. When the parasite is located in the nerve tissue, discrete fibrillary astrocytosis can be seen more externally. The second stage, or necrotic (colloid, granular) stage, corresponds to parasite necrosis and the associated inflammatory process. The necrotic cysticercus appears as an eosinophilic structure in which components of the bladder and scolex, in various stages of disintegration, are identifiable. In direct apposition to the necrotic parasite are multinuclear foreign-body type giant cells, foamy macrophages, and a small number of neutrophil granulocytes. Deposition of cholesterol crystals is also observed. Neoformation of dense, fibrous connective tissue, usually with a circinate contour, permeated or surrounded by lymphoplasmacytic inflammatory infiltrate and a few eosinophils can be seen surrounding the necrotic cysticercus (Figs. 7 and 8). The adjacent nerve tissue shows moderate to intense fibrillary astrocytosis. Edema and/or necrosis of the surrounding nerve tissue may be present in some cases, particularly in patients treated with praziquantel (a cysticidal drug) and who died shortly after, as well as in patients with a strong immune-inflammatory response (cysticercotic encephalitis) (1,60,65). With time, fibrosis develops progressively occupying the entire lesion. This stage can be macroscopically recognized as a nodule of a smaller size than the bladder in the preceding stage, with a whitish, white-grayish or grayish central area surrounded by a thin capsule of grayish or sometimes whitish color, corresponding to the necrotic cysticercus and fibrosis, respectively (Fig. 9). In the third and final stage, a fibrocalcified nodule is formed. Fibrosis occupies the entire lesion, associated or not with residual lymphoplasmacytic infiltrate (Fig. 10). The fibrous nodule thus formed frequently calcifies , as seen in 57.6 to 64.7% of NCC cases subjected to CT (48,80). Calcification may result 1) from partial dystrophic calcification of the necrotic larva, or 2) from the presence of cysticercal calcareous corpuscles. The latter may remain in the lesion for an indefinite period, thus permitting identification of the parasite in fibrocalcified lesions (10,57,63). Dystrophic calcification is a long-lasting process and may take 2 to 10 years to be detected on X-ray films. Macroscopically, the residual fibrocalcified nodule has a hard consistency and is smaller than the cyst observed in the preceding stage. In approximately 10% of NCC cases, it can only be identified by microscopic examination. Treatment with praziquantel or albendazol accelerates regression of the cysticercus, as confirmed by CT scans performed several weeks or months after the treatment is started (7,18,19,49,64,72,87).

C. racemosus induces a more intense inflammatory and fibrosing reaction (Figs. 11 and 12), the latter causing small loculi of connective tissue to be formed around the remnants of the bladder wall of the parasite (63). The more intense immune-inflammatory response suggests an active, continuous formation of new antigenic membranes, without the development of immune tolerance, commonly seen with *C. cellulosae.*

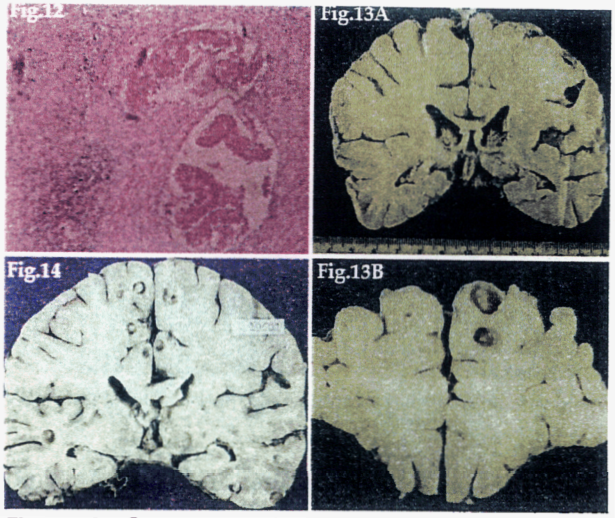


Figure 12. *C. racemosus*. A more advanced stage of the process shown on Fig. 11, with two small fibrotic loculi surrounding the remnants of the cyst wall. H&E, X113.

Figure 13. *C. cellulosae*. Asymptomatic form. Cysticerci in the subarachnoid space **(A)** and brain parenchyma **(B)**.

Figure 14. *C. cellulosae*. Convulsive form. Multiple cysticerci in the cerebral cortex and cortex/white matter junction.

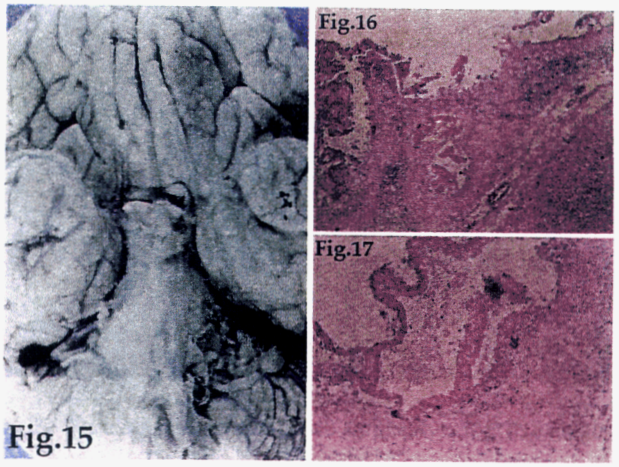


Figure 15. Cysticercotic leptomeningitis. Intense whitish thickening of the leptomeninges at the base of the brain.

Figure 16. Cysticercotic leptomeningitis. Intense inflammatory reaction and fibrosis of the leptomeninges surrounding remnants of *C. racemosus* cyst wall. The nerve tissue can be seen on the lower right. H&E, X45.

Figure 17. Cysticercotic leptomeningitis. Intense fibrosis and giant cell reaction surrounding remnants of *C. racemosus* cyst wall. Note the small protrusions on the external face of the necrotic tegument. H&E, X113.

Other CNS lesions associated with NCC can be found, depending on the type of cysticercus (*C. cellulosae* or *C. racemosus*), location of the parasite, and the host immune-inflammatory response. When located in the basal cisterns, the intense inflammatory and fibrosing reaction induced by *C. racemosus* often results in chronic leptomeningitis, with marked whitish thickening of the pia-arachnoid around the cysticerci, obstruction of the CSF drainage orifices in the fourth ventricle, internal hydrocephalus, and increased intracranial pressure (58,63,86). Ventricular location of the cysticercus frequently causes granular ependymitis. As the parasite dies, the inflammatory reactive intensifies and adherence of the parasite to the ventricular surface is aided by the reactional fibrillary astrocytosis which is continuous with granular ependymitis (58,63,86,92). Obstruction of the flow of CSF may occur when the cysticercus is located, for example, in the fourth ventricle. Arterial lesions of an inflammatory nature, as described by Askanazi at the end of the last century, may develop, particularly in the cases of *C. racemosus*-induced chronic leptomeningitis at the level of the basal cisterns. Thickening of the leptomeninges by inflammation and fibrosis causes entrapment and occlusion of the blood vessels that arise from the circle of Willis (17). The most frequent findings are fibrous thickening of the adventitia, thinning and focal destruction of the middle layer, areas of interruption and duplication of the internal elastica limitans, and intimal fibrosis of local vessels of small, medium and, rarely, large diameter (58,66,86). Lacunar infarcts in the territory of the lenticulostriate arteries and, less commonly, large infarcts involving the superficial or deep territory of the middle cerebral, internal carotid and anterior cerebral arteries, in this order of frequency (17,44,63,69,73), may develop. Other arterial lesions, such as presence of inflammatory infiltrate in almost all the layers, fibrinoid necrosis, atheroma-like deposits, and occlusive thrombosis, may occasionally be found.

Clinical Picture

NCC affects males slightly more frequently than females. It may occur at any age, but the majority of the cases are found in young and middle-aged adults (48,54,77,80). NCC may be asymptomatic or cause a variety of clinical manifestations. There is no typical symptomatology that permits characterizing this parasitosis (86). In addition, the combination of two or more symptoms is common. For this reason, NCC should always be considered in the differential diagnosis of neurological and neuropsychiatric diseases in endemic areas. This clinical polymorphism of NCC is determined by 1) the number of cysticerci; 2) location of the parasites in the CNS; 3) variety of cysticercus involved (*C. cellulosae, C. racemosus*); 4) the stage of development and involution of the parasite; and 5) intensity of the host immune-inflammatory response. Several classifications of NCC have been attempted, based on anatomical features - parenchymal, subarachnoid, intraventricular, and spinal (23); clinical symptoms - mental disturbances, localized syndromes, increased intracranial/spinal pressure syndrome (93); disease activity as evaluated by CT and CSF analysis - active and inactive forms (80); and

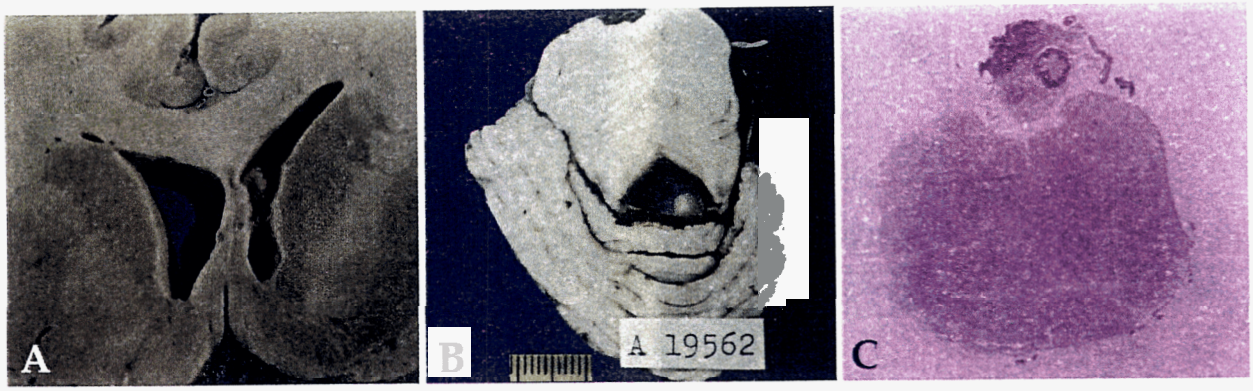


Figure 18. Intraventricular cysticercosis. *C. cellulosae* in the lateral ventricles **(A)** and fourth ventricle at the level of the pons **(B)** and medulla **(C)**. In the latter, the cysticercus is necrotic. H&E, X3.8.

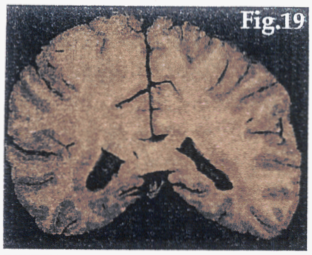
prognosis - benign and malignant forms (29). These two latter classifications do not differ significantly. Due to the complexity of NCC, none of these classifications is entirely satisfactory, as none succeeds in taking into account all factors that are responsible for the clinical polymorphism of the disease. Besides, a definitive categorization of NCC is made even more difficult by the coexistence of two or more clinical forms of the infection in the same patient. Since the clinical signs and symptoms, the topography and stage of development of the parasite, and the host immune-inflammatory response remain fundamental for an adequate diagnosis and treatment of NCC, a clinicopathologic classification is formulated herein, in which all of these elements are considered.

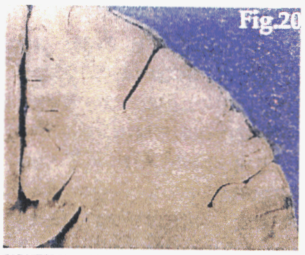
Clinicopathologic forms of NCC

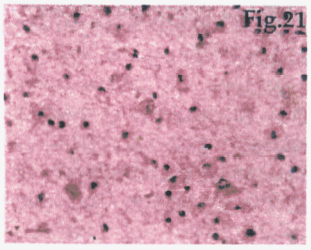
1. Asymptomatic form. In series of autopsies, this is the most commonly found form, corresponding to 80% of the cases of NCC (63). In series based on clinical diagnosis, 26 to 38% of the patients are asymptomatic (54,80). This difference is related to the selection of patients in each series, the former reflecting the low frequency of asymptomatic NCC in patients from a general hospital, and the latter pointing to the higher frequency of symptomatic NCC in patients from neurological and neurosurgery clinics. The usual site of the cysticerci in these asymptomatic forms (Fig. 13) is the subarachnoid space of the cerebral convexity and, less commonly, the brain parenchyma (cerebral cortex, cortex/subcortical white matter junction, and basal ganglia), and the lateral ventricles. Viable, necrotic or fibrocalcified cysticerci, solitary or in a small number, can be found in all of these locations.

2. Convulsive form. This represents the most frequent symptomatic form; it was identified in 52.4% of 753 patients with NCC (80). In 18-36% of the cases (48) seizures are the only clinical manifestation. In endemic regions, NCC is one of the major causes of late-onset epilepsy (50,54). Partial seizures with secondary generalization predominate in several series reported in the literature (54,80), whereas in other series generalized seizures are more common (22). Viable, necrotic or fibrocalcified cysticerci, solitary or multiple, located in the brain parenchyma (Fig. 14) are the most common finding in these patients (19,22,48,64,80). An increase in the frequency of seizures has been reported, coinciding with death of the cysticercus, as determined by magnetic resonance imaging - MRI - (79). Treatment with cysticidal drugs (praziquantel and albendazol) can reduce the frequency and severity of the seizures, and these may even disappear within months or years (18,19,22,49,87). This clinical improvement correlates with involution of the cysticerci, as evaluated by CT (18,19,49,64,72,87). In many patients, as the cysticercus calcifies, seizures tend to become less frequent and less severe 6 months after their onset, and they may even stop after a few years, even without cysticidal treatment (48).

3. Cysticercotic leptomeningitis. This is the second most frequent cause of symptomatic NCC; it is found in 48.2% of NCC cases (45,48,80). It is caused by the presence of *C. racemosus* in the basal cisterns, associated with intense inflammatory reaction and fibrosis, leading to progressive thickening of the leptomeninges at the base of the brain (Figs. 15-17). In approximately 57-67% of the cases, there is obstruction of the lateral and median openings of the fourth ventricle, resulting in internal hydrocephalus and increased intracranial pressure. Signs of meningitis and cranial nerve palsy are less commonly observed. Location of the cysticerci in specific areas of the leptomeninges can cause chiasmatic syndrome (progressive visual loss and homonymous hemianopsia) and cerebellopontine-angle syndrome (tinnitus, progressive deafness, loss of labyrinth functions, facial hyperestesia, reduced corneal reflex, facial palsy) (23,93). Cerebral infarcts, although less common (3.9%), may develop as a result of the frequent inflammation of medium-, small- and, more rarely, large-diameter local vessels (23,48). When hydrocephalus secondary to cysticercotic leptomeningitis is present, mortality is high (50%), and most patients die within 2 years after CSF shunting (81).







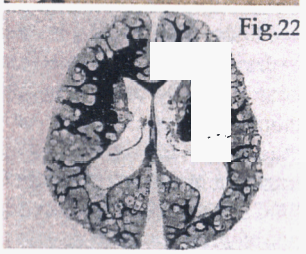


Figure 19. Cysticercotic encephalitis. Multiple necrotic nodules in the brain parenchyma (arrows).

Figure 20. Cysticercotic encephalitis. Detail of a cysticercus surrounded by necrosis.

Figure 21. Cysticercotic encephalitis. Area of necrosis, with macrophages and reactive fibrillary astrocytes. H&E, X450.

Figure 22. Disseminated cysticercosis. Uncountable viable cysticerci disseminated in the brain parenchyma, particularly in the cortical and subcortical white matter. Reproduced from Piazza R (1977) Atlas de Neuropatologia Psiquiátrica, Editora Manole: São Paulo.

4. Intraventricular cysticercosis. This variation represents 16% of the NCC locations reported in series of autopsies (63) and 0.7-12.6% of those observed in clinical series (48,80). It is characterized by the presence in the ventricular cavities, particularly the fourth ventricle (Fig. 18), of a cyst, usually solitary, of the *C. cellulosae* variety (more rarely of *C. racemosus*). Intermittent obstruction of the flow of CSF may occur, indicating cyst movement within the ventricles. Occasionally, the cerebral aqueduct may become obstructed by a cysticercus floating freely in the interior of the fourth ventricle, leading to transient episodes of increased intracranial pressure and loss of consciousness (or even sudden death) related to abrupt movements of the head - Bruns' syndrome (23,47,48,93,94). Permanent obstruction, of subacute onset, may occur when the larva dies and, during the healing process, adheres to the ventricular wall adjacent to the CSF drainage orifices and/or the frequently associated granular ependymitis (23,45). Patients with free-floating intraventricular cysts removed surgically usually have a better clinical course than those with cysts adhering to the ventricular wall, who must subsequently undergo ventriculoatrial/peritoneal shunting procedures (12).

5. Cerebrovascular cysticercosis. As previously mentioned, inflammatory arterial lesions affecting vessels of small, medium and, more rarely, large diameter, whether or not complicated by thrombosis, are common in the cases of *C. racemosus*-induced leptomeningitis. As a consequence, ischemia and cerebrovascular events may occur (2,17,69,93). These may be 1) lacunar infarcts in the territory of the lenticulostriate arteries, the most common complication, producing clinical symptoms such as ataxic hemiparesis, pure motor hemiparesis, or sensorimotor stroke; 2) large infarcts in the superficial or deep territory of the middle cerebral artery or the internal carotid artery, less frequently observed; 3) progressive midbrain syndrome, of rare occurrence, caused by involvement of the midbrain and thalamus due to occlusion of paramedian thalamopeduncular branches of the mesencephalic artery ; 4) transient ischemic attacks, equally rare, produced by cysticerci in periarterial location. Progressive midbrain syndrome is usually associated with cysticercotic leptomeningitis, with involvement of the interpeduncular and prepontine cisterns. Somnolence, paraparesis, impaired vertical gaze, dilated, fixed pupils, and urinary incontinence are the main clinical symptoms. This condition has been associated with a high mortality rate: 85% of the patients die after a protracted course. In large NCC series, the frequency of cerebrovascular diseases varies from 2.3 to 4.2% of the cases (48,77,80).

6. Cysticercotic encephalitis. This is a relatively rare form of CNS cysticercosis (23,65), found in less than 1% of the patients with NCC. It affects children, adolescents and young adults, predominantly of the female sex. The clinical picture consists of signs and symptoms of increased intracranial pressure, seizures, and diminution of the visual acuity lasting from 1 to 18 weeks, with a progressive or recurrent course. In a study of 8 patients, 2 died and the others had a generally favorable clinical course (65). Pathological examination of the brain showed diffuse cerebral edema and multiple necrotic cysticerci in the brain parenchyma, surrounded by edema and intense inflammatory infiltrate consisting of mononuclear cells and macrophages (Figs. 19-21). The host immune response is believed to cause necrosis of the cysticerci in these cases.

7. Disseminated cysticercosis. This rare form of NCC, which preferentially affects young adults, is characterized by the presence of hundreds of viable cysticerci in the brain (Fig. 22), associated with intense infestation of the skeletal muscles and subcutaneous tissue (88), and pseudo-hypertrophy of the muscles. Uncontrolled seizures and progressive dementia, without focal neurologic signs or evidence of increased intracranial pressure, are the major clinical symptoms. The association of seizures, progressive dementia and swelling of the skeletal muscles is exclusive to disseminated cysticercosis. Detection of palpable cysticerci in the subcutaneous tissue is suggestive of the diagnosis, prior to performance of a CT scan.

8. Demented form. The appearance of psychiatric disorders in NCC has been reported since the second half of the nineteenth century. In the recent litera-

ture, approximately 5.5 to 20% of the patients with NCC display mental disturbances, particularly dementia, almost always associated with seizures, cysticercotic leptomeningitis, and hydrocephalus (23,48,77,80,93). It is difficult to evaluate the real incidence of mental disturbances in NCC, not only because of the almost constant association with other pathologies that can cause them, but also because the existing studies are retrospective and the clinical evaluations were made by professionals with no training in Psychiatry. In endemic areas, NCC should be included in the routine differential diagnosis of neuropsychiatric diseases. Routine screening for NCC by serodiagnosis or CT is also recommended in psychiatric patients from endemic areas (83). On the other hand, individuals with NCC may be at a higher risk for neuropsychological dysfunction. A recent study suggests that behavioral functions that include aspects of inhibitory control, motor, and visual-motor output are impaired in adolescent and adult subjects with NCC (43).

9. Spinal cysticercosis. This is an equally rare form of NCC (1.6-5.4%). It results from the presence of cysticerci in the subarachnoid space or, still more rarely, in intramedullary locations (8,11,39,61,80). The thoracic and cervical segments are the most frequently affected. The epidural location is exceptional. The clinical manifestations are secondary to compression of the spinal roots/cord by cysticerci and to chronic arachnoiditis. Cysticerci in the subarachnoid space may cause root pain and weakness of the limbs, with a subacute and progressive course. The clinical manifestations in intramedullary cysticercosis are progressive motor deficit, usually spastic paraplegia, with a sensorial level and sphincter disturbances (23).

10. Combined forms. Two or more of the NCC forms described above, particularly the most common ones, may be associated in the same patient.

Diagnosis

The clinical diagnosis of NCC is often difficult, due to the polymorphic symptomatology of the disease (31). Physical examination and analysis of the patient's clinical history and life conditions may help in some cases, but the diagnosis depends basically on neuroimaging procedures and CSF analysis. (31,35). The identification of viable or necrotic cysticerci or fibrocalcified nodules containing calcareous corpuscles in fragments obtained at autopsy or during surgery permits establishing a definite diagnosis of NCC. The presence of solitary or multiple lesions revealed by neuroimaging procedures, combined with positive immunological CSF tests, makes the diagnosis probable. Demonstration by neuroimaging procedures of an area suggestive of cortico-subcortical calcification and the presence of inflammatory alterations in the CSF are supportive of a possible diagnosis of NCC. (Quagliato, 1992 - unpublished data).

CT and MRI have greatly improved the accuracy in the diagnosis of NCC. The neuroradiologic findings depend on the type of cysticercus, stage of larval development and involution, and location and number of cysts. On CT scans, the viable *C. cellulosae* appears as a hypodense, non-enhancing round lesion, solitary or multiple, 5-10 mm in diameter, containing a scolex (7,23,31,37, 41,48,52,56,70). The necrotic cysticercus is seen as a round, hypodense lesion surrounded by edema that enhances with contrast, usually in a ring-like pattern. In the nodular calcified stage, density of the calcification is greater than that enhanced by contrast. The injection of contrast medium is of great value in the diagnosis of NCC. The inflammatory reaction around the necrotic cysticercus leads to rupture of the blood-brain barrier, allowing the contrast medium to penetrate around the lesion, thereby enhancing it. In addition to demonstrating the cysticerci, CT permits identifying other lesions associated with NCC, such as leptomeningitis, hydrocephalus, infarcts, and cerebral edema (23). *C. racemosus* can be more easily visualized on CT scans when the image is that of a cluster of multilocular cysts arranged like a "bunch of grapes" (68).

MRI is superior to CT in demonstrating viable cysticerci, and is also more appropriate for evidencing the scolex within the cyst. T1-weighted images can show integral, viable cysts which do not enhance after contrast injection, as well as disintegrating, necrotic cysts in which the surrounding inflammatory reaction is enhanced by contrast, producing a ring-like or nodular image (15,79,84,92). MRI also permits demonstrating a larger number of cysticerci than CT. Besides, other lesions associated with NCC, such as leptomeningitis, are well demonstrated by MRI, and are seen as contrast enhancement of the leptomeninges at the level of the circle of Willis and sylvian fissure (44,73).

CSF analysis, together with the clinical data and neuroimaging findings, is essential for the diagnosis of NCC. The appearance of inflammatory cells and specific antibodies in the CSF coincides with death of the cysticercus and intensification of the host immune-inflammatory response, particularly when the parasite is lodged in the subarachnoid space and produces leptomeningitis (48,80). In these cases, protein levels are elevated and there is an increase in cellularity, with neutrophilia, lymphocytosis, and eosinophilia. Eosinophilia is present in 57.3% of the patients with and in 4.3% of the patients without CSF inflammatory changes (80). The tests available for CSF immunodiagnosis include 1) complement-fixation reaction; 2) indirect immunofluorescence; 3) passive hemagglutination; and 4) immunoenzimatic assays (enzyme-linked immunosorbent assay-ELISA-, dot blot, immunoblot), which have greater specificity and sensitivity as compared with the other tests.

Several antigens with an increasingly higher degree of purity have been obtained from the total cysticercus, scolex, vesicular fluid, vesicular membrane or from a combination of these, for utilization in enzymatic assays (4,25,28,35,42,55,59,71).

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