IMMUNOLOGY OF TAENIA SOLIUM TAENIASIS AND HUMAN CYSTICERCOSIS

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Abstract

The life cycle of *Taenia solium*, the pork tapeworm, is continuously closed in many rural settings in developing countries when free roaming pigs ingest human stools containing *T. solium* eggs and develop cysticercosis, and humans ingest pork infected with cystic larvae and develop intestinal taeniasis, or may also accidentally acquire cysticercosis by fecal-oral contamination. Cysticercosis of the human nervous system, neurocysticercosis, is a major cause of seizures and other neurological morbidity in most of the world. The dynamics of exposure, infection and disease as well as the location of parasites result in a complex interaction which involves immune evasion mechanisms and involutive or progressive disease along time. Moreover, existing data is limited by the relative lack of animal models. This manuscript manuscript revises the available information on the immunology of human taeniasis and cysticercosis.

LIFE CYCLE, EPIDEMIOLOGY, AND CLINICAL MANIFESTATIONS

Life Cycle

Taenia solium, the pork tapeworm, is a cestode (flatworm) parasite whose life cycle is continuously closed in many rural settings in developing countries when free roaming pigs ingest human stools containing *T. solium* eggs and develop the larval infection, becoming intermediate hosts, and humans ingest pork infected with cystic larvae and develop intestinal taeniasis.(1, 2)

When pork contaminated with parasitic cysts is ingested by a human, the cyst's scolex evaginates by action of bile and intestinal enzymes, and affixes to the mucosa of the human

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small intestine. Here the worm grows by reproducing its cells at the neck level, developing segments or proglottids which mature as they become more distal to the scolex. The adult *T. solium* measures between 2 to 4 meters in length.(1, 3) The tapeworm is hermaphroditic and after fertilization the final segments are gravid and full of mature eggs. These infective eggs are expelled to the environment with the feces of the tapeworm carrier. Once ingested by a suitable host (usually the pig), the embryos contained in the eggs hatch, cross the intestinal wall, and are carried by the bloodstream to all body tissues where they establish as the larval stage or cysticercus. Humans get infected with cysticercosis via fecal oral contamination. Thus humans may have adult intestinal tapeworm (taeniasis), or larval (human cysticercosis) infections, while pigs only act as intermediate hosts (porcine cysticercosis).(4)

Geographical Distribution

Taeniasis/cysticercosis is endemic in Latin America, Sub-Saharan Africa, India, vast parts of China, and South East Asia.(5–7) Cysticercosis cases are also seen with some frequency in non endemic countries in North America, Europe and Muslim regions because of travel and immigration from endemic countries, as clearly demonstrated in an outbreak of cysticercosis in Orthodox Jews in New York city.(8) The infection and subsequent disease result in significant costs both from health and other costs related to symptomatic disease and from losses to farmers because of porcine cysticercosis.(9–11)

The large and very similar tapeworms *Taenia solium, Taenia saginata*, and *Taenia asiatica* may coexist in some geographical areas.(12, 13) It has been suggested that the co-existence of other close taenid species may somehow reduce or restrict *Taenia solium* transmission. (14)

Clinical manifestations

While intestinal taeniasis is basically asymptomatic,(15) cysticercosis cysts in the nervous system produce neurocysticercosis (NCC), which is responsible for most of the burden of human disease. Seizures are the commonest clinical manifestation and in fact NCC is considered the major cause of adult onset seizures worldwide. The overall contribution of NCC to the prevalence of epilepsy in endemic regions is estimated to be around 30% of all epilepsy cases.(16, 17) Surveys in endemic regions using serology or CT consistently demonstrate two or three times more evidence of infection in individuals with epilepsy than in comparable asymptomatic populations.(17–23) Risk factors for cysticercosis include a history of intestinal taeniasis, pig raising, and poverty-related factors including living in a rural area and poor sanitation.(24)

The clinical manifestations of symptomatic human NCC reflect the number, location, size and evolutionary stage of the parasites, as well as the presence and degree of the inflammatory response of the host. Parasitic larvae located in the parenchyma of the brain most frequently manifest with seizures. They establish as viable cysts, and after an extremely variable period (which may be decades) follow an involutive process, driven by the attack of the immune response of the host. Whether this process is always a consequence of the death of the parasite is unlikely since in a placebo-controlled study of antiparasitic treatment of patients with viable NCC cysts 87% of the cysts were still viable 6 months later.

(25) Initially the viable cysts are rounded vesicles of parasitic membrane filled with clear fluid, containing a scolex or tapeworm head. Following the host's attack the cysts contents become turbid, the membrane and scolex degenerate by the action of the cellular response, and the cyst structures shrink and are replaced by hyaline and fibrotic tissue to later disappear or leave a residual calcified scar.(26, 27) Parasites in the subarachnoid space follow a different course and tend to grow and infiltrate, becoming mass occupying lesions and blocking the circulation of the cerebrospinal fluid with subsequent hydrocephalus. Unlike intraparenchymal NCC; subarachnoid disease is progressive and associated with significant mortality.(28–30)

IMMUNOLOGY OF HUMAN CYSTICERCOSIS

Exposure to the parasite

In *Taenia solium* endemic regions, exposure of the human population to the parasite is a very frequent event. Between 10 and 25% of all villagers show specific anti *T. solium* serum antibody responses in the very specific enzyme-linked immunoelectrotransfer blot assay using lentil-lectin-purified glycoprotein antigens (LLGP-EITB).(5, 31) This is clearly an underestimation of the proportion ever exposed since a sizable group of people, up to 50% of those seropositive, will turn seronegative in a short term (transient antibodies).(32–34) It follows that at population level *T. solium* human infection is a very dynamic process. Most if not all seroepidemiological studies have used antibodies to the cyst stage. Antibodies to the oncospheral stage, which should arise much early in the infection process, have been identified.(35) However, no population studies of transmission dynamics using antibodies to the oncospheral stage are available. How previous exposures to the parasite affect the likelihood of successful infection in further challenges is not known.

Established infection

Very likely most of the invading oncospheres are destroyed while passing through the liver, or early at arrival in non-immunologically privileged sites.(4, 36) Some oncospheres survive, preferentially in protected places like the central nervous system or the eye. Still, human infection is a frequent event which in most cases courses and resolves without obvious symptoms, as proven by the sizable proportion of people showing residual brain calcifications in endemic populations. Consistently, epidemiological studies using brain CT (or more rarely using MRI), finding that 10 to 20% of villagers have brain cysticercosis, most of them with only one or a few calcified scars and no clinical disease.(37–41) Most cases of human infection in population based studies correspond to these calcified lesions. The proportion of people who show viable NCC in non-symptomatic individuals in population-based studies is much smaller, usually below 1%.(40) An Indian study using MRI in a highly endemic population reported 5% of asymptomatic individuals having one or two small brain cysts.(42) So far, no other studies have replicated these findings. Also there is basically no information on how many people could have cysticercosis in sites other than the nervous system in a population setting.

Exposure, infection, established viable infection, and symptomatic disease

While exposure and resolved infections are a frequent event in human populations, infections with viable parasites are present in smaller proportions in asymptomatic individuals (<10% of all imaging positive).(40) In clinical series, conversely, viable NCC cases comprise the majority of cases,(24) suggesting that established viable infections are associated with a higher likelihood of symptoms and more severe disease.

Evolution of human neurologic and extraneural infection

Available information on the evolution of human infections comes from large case series described more than a century ago.(43–45) These case series are from neurological patients so neurocysticercosis is the dominant presentation, although exhaustive search identified residual calcifications in muscles or in subcutaneous tissues in many cases.(45) From the few patients with concomitant subcutaneous cysticercosis it is apparent that subcutaneous nodules are noticeable months or years before neurological symptoms appear.(45) Also necropsy series demonstrate that in most cases cysts in tissues other than the nervous system had resolved while brain cysts are still viable.(43, 44) Patients may host viable parenchymal cysts for many years, even decades. Patients with subarachnoid neurocysticercosis manifest with mass effects or intracranial hypertension at older ages. Overall, the fragmentary available information suggests that embryos get distributed by the circulatory system to all tissues, and survive preferentially in the nervous system where they can be alive for many years or even be the cause of progressive disease as it commonly occurs in subarahnoid NCC.

Immune response by type of NCC

In general, extraparenchymal NCC (cysts in the ventricles or subarachnoid space) is associated with high parasite antigen levels, an exuberant immune response expressed as very strong antibody reactions.(30, 46) and marked local inflammation with mononuclear CSF pleocytosis and increased proteins. Conversely, the degree of immune response in patients with only intraparenchymal lesions is dependent on the number (and likely the volume) of the lesions as well as their stage of involution. Antigen levels and antibody responses may not be detectable in up to 40% of individuals with a single degenerating parasite, while individuals with multiple viable cysts are consistently seropositive and their antigen levels correlate with the numbers of parasites.(47, 48)

Immunopathogenesis

The *T. solium* cysticercus uses a series of active immune evasion mechanisms which include protection by local barriers (such as the blood brain barrier or the hemato-ocular barrier), blockage of the complement system, secretion of cytokines affecting the cellular response, safe degradation of host immunoglobulins, or masking itself with host immunoglobulins to evade immune surveillance.(49–55)

Intraparenchymal NCC—Most available information refers to intraparenchymal NCC. Once the cysts establish in the nervous system, it was originally felt that a Th2 type response was established with low IFN g and IgG2a antibodies and increased IgG1, IgE, IL 4, IL 13

and IL 15.(39, 56–62). However, it rapidly became apparent that the acquired T cell response was mixed in the murine model of infection using *T. crassiceps* with a mixed Th1 and Th2 phenotype.(63) A similar mixed picture was reported in pigs vaccinated against *T. solium* with the suggestion that the Th1 cytokines were associated with a post-vaccination inflammatory response.(64) In man, where a mixed Th1/Th2 response is also found,(65, 66) the presence of Th2 cytokines have been associated with asymptomatic disease suggesting that these cytokines reduce inflammation whatever the anatomical location of cysts.(67) Protective induction of Th2 responses has been shown in other tissue larval helminth infections including schistosomiasis,(68) *Echinococcus multilocularis*,(69) and others. Osteopontin may have a role in down-regulating the inflammatory Th1 response(70) although other endocrine mediators including sex hormones may also be involved.(71) Little is known about other T cell subsets in neurocysticercosis although IL-17, the prototypic Th17 cytokine, has been reported in infection (71) and recently Tregs have been found in the CNS and appeared to be important in limiting inflammation.(72)

More recently, alternatively activated macrophages have been proposed to contribute in maintaining this stage.(73, 74) Immune modulation is lost once the host discovers the parasitic cyst naturally(75) or more markedly after antiparasitic treatment. At this point the chemokine profile switches back to Th1-like and the host's inflammatory response attacks and destroy the parasite. Perilesional inflammation is a major contributor to seizures and other symptoms in intraparenchymal NCC.(76, 77) The pro-inflammatory response is in part mediated via MyD88 pathway a key regulator of cytokines such as TNF, IL-1B and IL-6 gene expression and secretion in monocyte-derived cells including microglia.(78) We demonstrated that in human monocytes chemokine secretion in response to cyst antigens is dependent on the transcription factor NF-kB but independent of TLR-4.(79) Monocyte-astrocyte networks may be key in amplifying the pro-inflammatory response.(80) However, whether this pathway is directly associated with seizure activity has been questioned in the murine model.(81)

In addition to cytokines, immune mediators involved in migration and adhesion of inflammatory leukocytes are also up-regulated in neurocysticercosis although data are relatively sparse. Soluble intercellular adhesion molecule (sICAM)-1 was elevated in patients with symptomatic neurocysticercosis.(82, 83) There are no data on other adhesion molecules or on conformational changes in their ligands, the integrins.

Although cytokines and other immune mediators are important in driving the pro-inflammatory response, tissue damage observed on CT scans and increased permeability of the blood brain barrier implies the involvement of enzymes driving tissue destruction. The blood brain barrier is rich in type 4 collagen which is one of the substrates of matrix metalloproteinase (MMP)-9. The MMPs are a family of zinc-containing enzymes potentially able to degrade all components of the extra-cellular matrix.(84) They are secreted usually as pro-forms by a large variety of cells including those of the monocyte lineage and stromal cells. MMPs are tightly transcriptionally regulated and also blocked by specific Tissue Inhibitors of Metalloproteinases (TIMPs). MMP-9 or gelatinase B has been associated with both breakdown of the blood brain barrier in the murine model of neurocysticercosis(85, 86) and there are data consistent with this observation from patient studies(87, 88) Of particular

interest was the observation that the non-specific MMP inhibitor doxycycline reduced leukocyte-dependent inflammation in the murine model of neurocysticercosis.(89) In addition to its known antibiotic activity, doxycycline is licensed as a non-specific MMP inhibitor for use in periodontal disease in the USA and these emerging data suggest that anti-MMP therapy or possibly blockade of the upstream signaling pathways may be an effective way to control inflammatory tissue damage in neurocysticercosis.

Extraparenchymal NCC—There two major types of extraparenchymal NCC. In intraventricular disease, parasites are usually cystic in nature (spherical, most times with a visible scolex), and most of the clinical manifestations are caused by direct blockage of the CSF circulation and the resulting obstructive hydrocephalus. There is an associated inflammatory component and high dose steroids frequently contribute to improve the patient situation. Steroids should always be administered in the settings of appropriate control of intracranial hypertension and shunt placement where indicated. We have found that cyst fluid contains an anti-inflammatory IL-10-like mediator which is lost during inflammation associated with anti-parasitic therapy which results in increased pro-inflammatory chemokine secretion in response to scolex and membrane antigens.(90)

In subarachnoid NCC (basal or of the Sylvian fissure), the lesions demonstrate an exuberant growth of the cystic membrane, many times forming clumps of vesicles (hence the old name of recemose cysticercosis, because of its similitude to a bunch of grapes) in which many times no scolex is visible. This type of NCC occurs in patients quite older than those with intraparenchymal NCC.(28)

Coinfections with NCC and other agents

The coexistence of NCC and HIV has been reported in multiple occasions.(91, 92) While some of these patients had severe forms of NCC, and some authors hypothesized that HIV infection could be associated with more severe NCC, no controlled data exist to support this affirmation.(93, 94) Another co-infection reported multiple times is the coexistence of NCC with Japanese encephalitis. Lesions of both diseases tend to occur in the same hemisphere, and it is also assumed that NCC predisposes to more severe disease in Japanese encephalitis. (95–97)

IMMUNOLOGY OF THE INTESTINAL TAPEWORM STAGE

Adult tapeworm infections are present in a small proportion of individuals in endemic regions, usually between 0.5% to 2% of the population.(7, 98) The enormous biotic potential of *T. solium* allows this small population of tapeworms to infect many pigs and thus ensure the survival of the species.

Life span of the tapeworm

It was initially believed that the adult *Taenia solium* tapeworm lived for many years. This seems to have been based on anecdotal case reports most likely corresponding to other tapeworms. Clinical evidence do not support this claim. The tapeworm carrier is the person most exposed to infection, however only a few patients with NCC carry a tapeworm by the

time of diagnosis.(99) In the classic reports of the British military "outbreak" (in which 454 British soldiers or immediate relatives developed neurological disease due to cysticercosis after returning from their tour of duty in India, data which nicely demonstrated that a significant majority of cases presented symptoms between 2 to 5 years after exposure),(44, 45, 100) very few tapeworm carriers were detected, suggesting that most tapeworms would live less than 5 years. Epidemiological data also supports this concept. In the largest series of *Taenia solium* taeniasis infections published, Allan *et al* presented a curve of taeniasis prevalence by age which sharply decreases after age 30,(101) where a sharp decrease in prevalence at a given age period is unlikely to occur in a long lived infection. Also, seizure cases do not cluster around tapeworm carriers(102) reflecting a changing tapeworm population.

Interaction with the host

The *T. solium* tapeworm lodges in the upper small intestine and uses its four suckers and its double crown of hooks to anchor in the intestinal mucosa.(103) Once the suckers attach to the villi, the rostellum projects into the mucosa and the hooks extend, fixing the scolex to the intestine. There is local damage and an inflammatory response which involves mast cells and goblet cells, and varied cell populations including plasma cells, lymphocytes, neutrophils and eosinophils.(55)

Stage-specific antibody responses have been identified in serum from tapeworm carriers (see below under diagnosis of taeniasis). *T. solium* calreticulin, a calcium binding protein which preferentially localizes in the rostellum and suckers, has been explored as a potential oral vaccine to increase the local intestinal mucosal response to an incoming tapeworm.(104) After immunization with this protein, evidences of partial protection have been obtained in two different rodent models, hamsters and gerbils.(105, 106) In the related tapeworm *Echinococcus granulosus*, two different research groups have demonstrated significant protection after vaccination of the definitive host, the dog.(107–109)

In summary, human taeniasis/cysticercosis is a very complex example of host-parasite interaction where the immune response of the host and the extent and nature of the inflammatory reaction, with active immunomodulatory mechanisms enacted by the parasite, determine the symptomatic expression of clinical disease. Our understanding of the specific mechanisms involved in this interaction is limited by the inherent variability of infections in terms of infective dose, number, size and location of the parasites (with the consequent extreme variability of its clinical expression), the very high frequency of exposure of individuals and animals to the parasite in endemic regions, the long period between infection and disease, and also by the lack of appropriate animals models.

Acknowledgments

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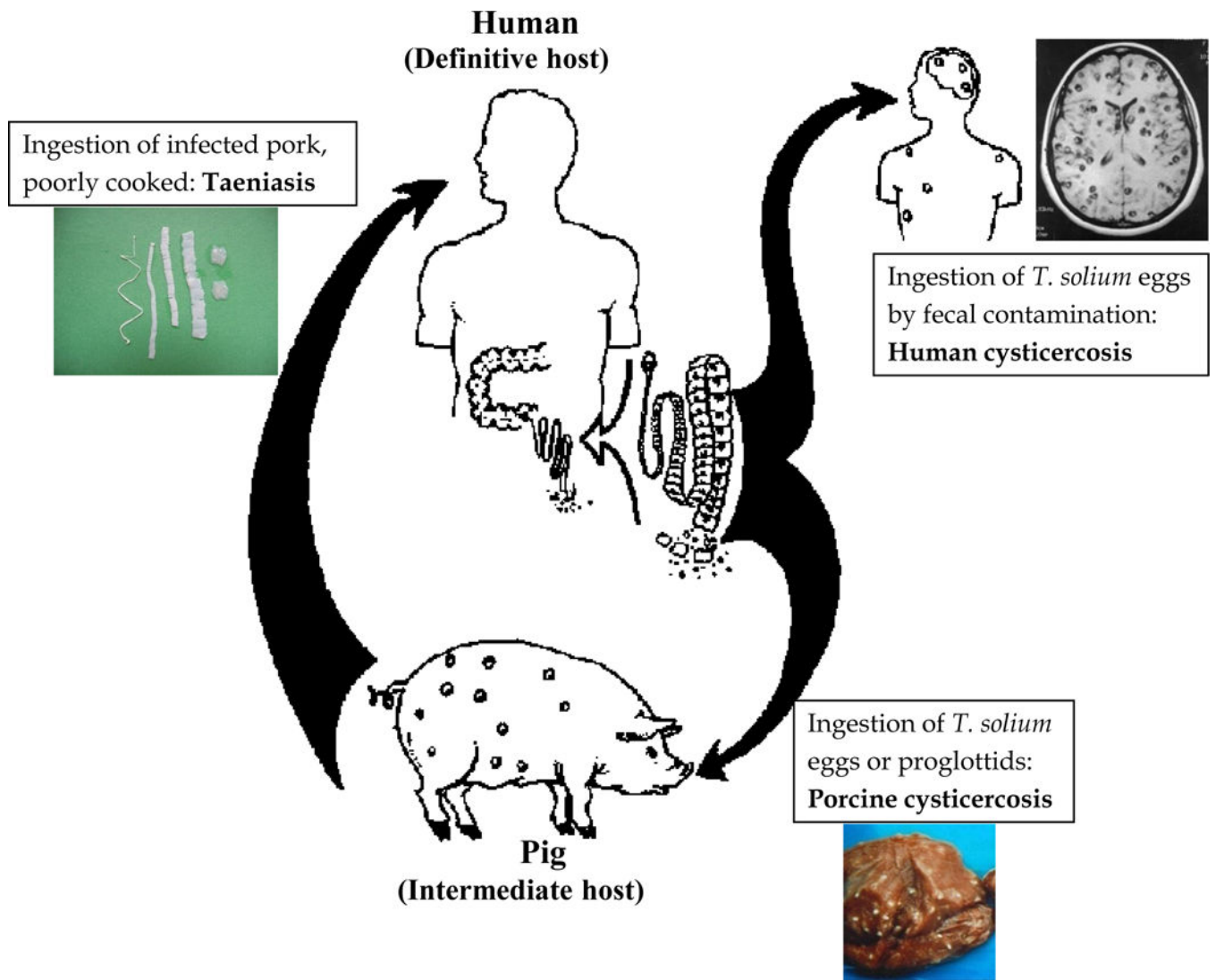
Figure 1.
Life cycle of *Taenia solium* (adapted with permission from Garcia HH and Martinez SM. *Taenia solium* taeniasis/cysticercosis, Lima, Ed. Universo; 1999: 360 p.)
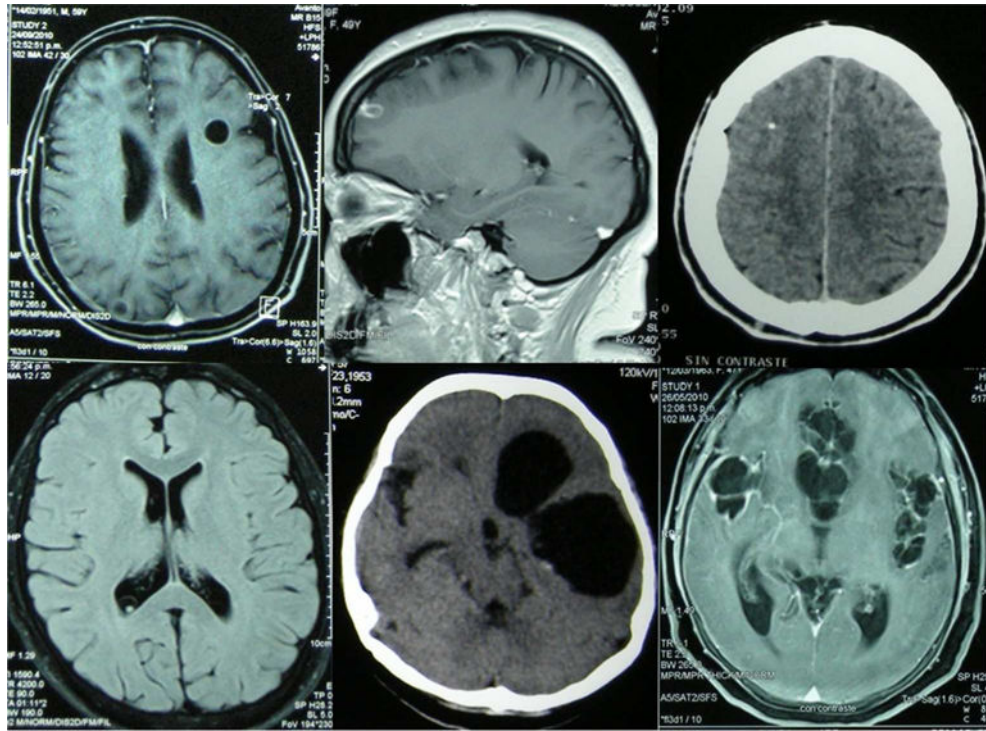
Figure 2.
Intraparenchymal neurocysticercosis: typical images of viable (top left), degenerating (top center), and calcified (top right). Extraparenchymal neurocysticercosis: intraventricular cyst (bottom left), a cyst mass in the Sylvian fissure (bottom center), and basal subarachnoid cysticercosis (bottom right).