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# Essential Neuroparasitology

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**Dedication**

**To my mother, father, brothers, sisters and sons**

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**Acknowledgement:**

**To my teacher Dr: Awad Ahmed Nasr, who helped and encouraged me to be a successful scientist.**

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## Introduction

Behavior-altering parasites are parasites capable of causing changes in the behavior of their hosts by directly affecting the hosts' decision-making and behavior control mechanisms. The acquired or modified behaviors assist in the parasite's transmission, and in the case of parasitoids result in the host's death. (1)

Parasites often have striking effects on the behavior of their hosts. These behavioral changes can be classed as adaptations on the part of the host, on the part of the parasite, or as nonadaptive byproducts of infection. In many cases it seems that these changes in behavior are adaptive for the parasite because they appear to facilitate transmission of the parasite to the next host in the parasite's life cycle. However, caution must be used in inferring that adaptive behavioral manipulation is occurring because simple byproducts of infection can have transmission-enhancing effects. In fact, in instances where host behaviors are altered, parasites that appear to benefit from behavioral changes often have less dramatic effects on host behavior than parasites that do not appear to benefit from altered behaviors. (2) Parasites often alter the behavior of their hosts in ways that are ultimately beneficial to the parasite or its offspring. (3)

The protozoan Toxoplasma gondii infects animals from the Felidae family (its definitive host), and its oocysts are shed with the host's feces. When a rodent consumes the fecal matter it gets infected with the parasite (becoming its intermediate host). The rodent subsequently becomes more extroverted and less fearful of felines, increasing its chance of predation and the parasite's chance of completing its lifecycle. There is some evidence that T. gondii, when infecting humans, alters their behavior in similar ways to rodents; it has also been linked to cases of schizophrenia. Other parasites that increase their host's risk of predation include Euhaplorchis californiensis, Dicrocoelium dendriticum, Myrmeconema neotropicum and Diplostomum pseudospathaceum.

Plasmodium falciparum, carried by the Anopheles gambiae mosquito, changes its host's attraction to sources of nectar in order to increase its sugar intake and enhance the parasite's chance of survival. It also decreases the host's attraction to human blood while gestating, only to increase it when it's ready to transmit to a human host.

Some parasites alter host behavior by infecting neurons in the host's central nervous system. The host's central nervous system responds to the parasite as it would to any other infection. The hallmarks of such response include local inflammation and the release of chemicals such as cytokine. The immune response itself is responsible for induced behavioral changes in many cases of parasitic infection. Parasites that are known to induce behavioral changes through central nervous system inflammation in their hosts include Toxoplasma gondii in rats, Trypanosoma cruzi in mice and Plasmodium mexicanum in the Mexican lizard.

While some parasites exploit their hosts' typical immune responses, others seem to alter the immune response itself. For example, the typical immune response in rodents is characterized by heightened anxiety. Infection with Toxoplasma gondii inhibits this response, increasing the risk of

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predation by T. gondii's subsequent hosts. Research suggests that the inhibited anxiety-response could be the result of immunological damage to the limbic system. (1)

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## Toxoplasmosis

A single-celled parasite called Toxoplasma gondii causes a disease known as toxoplasmosis. While the parasite is found throughout the world, more than 60 million people in the United States may be infected with the Toxoplasma parasite. Of those who are infected, very few have symptoms because a healthy person's immune system usually keeps the parasite from causing illness. However, pregnant women and individuals who have compromised immune systems should be cautious; for them, a Toxoplasma infection could cause serious health problems. (4)

Toxoplasma gondii, a protozoan parasite of mammals, is transmitted when oocytes excreted by cats or present in undercooked meat are ingested. Invasive forms enter the bloodstream to reach the brain, heart and lungs, where they form cystic aggregates that remain latent, but are subject to reactivation throughout the life of the host. In many communities most people have been infected by early childhood, but otherwise healthy persons do not develop clinically evident disease. In HIV-infected patients, however, toxoplasmosis holds serious implications:

• Primary infection may result in focal necrotizing encephalitis and occasionally retinochoroiditis and pneumonitis as a result of the unrestrained multiplication of tachyzoites.

• Reactivation of latent bradyzoites produces focal neurological signs mainly in patients with a CD4+ count of less than 100/mm3. Hemiparesis, cognitive disorders, seizures and other signs suggestive of an intracerebral space occupying lesion tend to develop subacutely over several weeks, and they are sometimes accompanied by symptoms of a diffuse encephalopathy. Fever and headache can be prominent, but meningeal irritation is infrequent. Changes in the cerebrospinal fluid are usually non-specific.

• Congenital transmission of T. gondii can occur as a consequence of either a latent infection or a new primary infection in the mother. In many instances the parasite induces spontaneous abortion or foetal death. Children born with signs of infection are generally severely ill, often with a potentially fatal syndrome characterized by hydrocephalus, hepatosplenomegaly with jaundice, mental retardation and chorioretinitis. Congenital disease that becomes apparent only later in life is usually less severe, but ocular or neurological impairment is common. (5)

Toxoplasmosis may cause flu-like symptoms in some people, but most people affected never develop signs and symptoms. For infants born to infected mothers and for people with weakened immune systems, toxoplasmosis may cause serious complications.

If you're generally healthy, not pregnant, and have been diagnosed with toxoplasmosis, you probably won't need any treatment other than conservative management. If you're pregnant or have lowered immunity, you may need medical management to avoid severe complications. The best approach, though, is prevention.

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**Symptoms**

Most healthy people who are infected with toxoplasmosis have no signs or symptoms and aren't aware that they're infected. Some people, however, develop signs and symptoms similar to those of the flu, including:

•Body aches

•Swollen lymph nodes

•Headache

•Fever

•Fatigue

**In people with weakened immune systems**

If you have HIV/AIDS, are receiving chemotherapy or have recently had an organ transplant, a previous toxoplasma infection may reactivate. In that case, you may develop more-severe signs and symptoms of infection, including:

•Headache

•Confusion

•Poor coordination

•Seizures

•Lung problems that may resemble tuberculosis or Pneumocystis jiroveci pneumonia, a common opportunistic infection that occurs in people with AIDS

•Blurred vision caused by severe inflammation of your retina (ocular toxoplasmosis)

**In babies**

If you become infected for the first time just before or during your pregnancy, you can pass the infection to your baby (congenital toxoplasmosis), even if you don't have signs and symptoms yourself.

Your baby is most at risk of contracting toxoplasmosis if you become infected in the third trimester and least at risk if you become infected during the first trimester. On the other hand, the earlier in your pregnancy the infection occurs, the more serious the outcome for your baby.

Many early infections end in stillbirth or miscarriage. Infants who survive are likely to be born with serious problems, such as:

•Seizures

•An enlarged liver and spleen

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•Yellowing of the skin and whites of the eyes (jaundice)

•Severe eye infections

Only a small number of babies who have toxoplasmosis show signs of the disease at birth. Often, infants who are infected don't develop signs — which may include hearing loss, mental disability or serious eye infections. (6)

Neurotoxoplasmosis, also known as cerebral toxoplasmosis, is an opportunistic infection caused by the parasite Toxoplasma gondii. It typically affects patients with HIV/AIDS and is the most common cause of cerebral abscess in these patients. (7)

**Effect on the brain:**

Once it enters the body, T. gondii traverses the intestinal or placental epithelium as a free parasite by paracellular transmigration and enters circulating cells such as macrophages or dendritic cells. It then appears to use such cells as a "Trojan horse" to gain access to privileged sites such as the brain.

In vitro studies using mouse brain cells have demonstrated that tachyzoites invade microglia, astrocytes and neurons and the parasite thereafter forms cysts within these cells. An in vitro study using human neurons and astrocytes showed that T. gondii also forms cysts in these cells. Human cell division autoantigen-1 was recently identified as a key host determinant of bradyzoite development within human fibroblasts. Electron microscopy studies on brains of chronically infected mice demonstrated that the majority of cysts are in neurons the cysts were identified within axons, dendrites, or the cell body of the neurons. In mice with congenital toxoplasmosis, cysts were also found within neurons in their brains. In humans, proliferating tachyzoites have been detected in glial cells in a patient who had developed toxoplasmic encephalitis. In another case of toxoplasmic encephalitis, T. gondii bradyzoites were observed in a Purkinje cell in the cerebellum. Toxoplasma gondii cysts have also been reported in astrocytes in humans; in that study, astrocytes were the only cell type that could be identified due to the poor preservation of the samples. Collectively, these studies demonstrate that T. gondii can infect a variety of brain cells, but additional studies are needed to identify the host cells that preferentially harbor cysts within the brain.

The effects of T. gondii on brain cells can be almost immediate, as shown by the work of Blader et al who used tachyzoites of a type II strain to examine host gene expression profiles in infected human fibroblasts. Within the first 2 hours of infection, although <1% of the 22 000 known human genes examined were upregulated by >2-fold, almost half of the affected genes encoded proteins associated with the immune response. Included among the upregulated genes were those encoding chemokines (GRO1, GRO2, LIF, and MCP1) designed to recruit immune cells, cytokines (IL-1β and IL-6) capable of activating immune responses, and transcription factors (REL-B, NF-κBp105, and I-κBα) that can promote expression of additional immune regulators. Thus, it is clear that the host cell mounts a strong response directed at alerting and activating the immune system to react to the infection.

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Twenty-four hours postinfection, by which time the parasite has replicated 2–4 times, a variety of host glycolytic and mevalonate metabolic transcripts are upregulated, presumably, in response to the nutritional drain imparted by the infection. Intracellular tachyzoites are also known to manipulate a variety of signal transduction pathways related to apoptosis, antimicrobial effector mechanisms and immune cell maturation. The recent finding of delivery of protein phosphatase 2C released from rhoptries of tachyzoites into the host nucleus will likely be a key step forward toward understanding the molecular basis of such transcriptional manipulation. Although similar studies on brain cells have not been reported, it seems likely that T. gondii infection may also influence signaling pathways in the brain.

There is only limited information on manipulation of host cells by bradyzoites. Foudts and Boothroyd recently reported that many of the same host genes (e.g., cytokines and chemokines) are affected by infection with bradyzoites or tachyzoites in human fibroblasts; however, the number of genes and the magnitude of activation were both lower in bradyzoite infection. Future gene expression studies on tachyzoite and bradyzoite infection of brain cells may reveal cell type–specific changes influencing the secretion of not only cytokines and chemokines but also neurotransmitters, receptors, ion channels, and other central components of brain physiology.

Elevated anti-T. gondii IgG antibody levels have been reported in patients with first-onset schizophrenia, suggesting an involvement of this parasite in the etiology of schizophrenia. Elevated serum levels of IL-1β have also been detected in individuals with acute schizophrenia, but not chronic schizophrenia and there were no differences in IL-1β or IL-6 serum or cerebro-spinal fluid levels in medicated patients compared with a control group. Because tachyzoites induce more pronounced inflammatory cytokine responses in host cells than do bradyzoites, as described above, proliferation of tachyzoites in the brain may be related to the onset of schizophrenia. The lack of elevated IL-1β or IL-6 in medicated patients could be due to the antitoxoplasmic activity of some antipsychotic drugs. Interestingly, anti-T. gondii IgM antibody, a key indicator of acute acquired infection, is not elevated in the sera of patients with first-onset schizophrenia, implying that the patients are not in the acute stage of a newly acquired infection. Therefore, a reactivation of chronic infection with the parasite (proliferation of tachyzoites caused by cyst rupture) in the brain might be involved in the onset of the disease. In support of this possibility, expression levels of proinflammatory cytokines, including IL-1β and IL-6, are higher in the brains of a mouse strain in which tachyzoite proliferation occurs in this organ during the later stage of infection compared with the brains of another mouse strain that prevents tachyzoite proliferation during chronic infection. It is noteworthy that individuals with congenital T. gondii infection often develop ocular toxoplasmosis later in life, and the disease is considered to be due to reactivation of infection. The onset of toxoplasmic chorioretinitis is most frequent during the ages of correlating well with the age of onset of schizophrenia. Therefore, congenital infection with T. gondii may be involved in the etiology of schizophrenia. [(8)]

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**Clinical presentation:**

In immunocompetent patients, acute encephalitis is extremely rare. Even in the immunocompromised symptoms are typically vague and indolent. Development of new neurological symptoms in these patients should raise high suspicion of cerebral toxoplasmosis.

**Pathology:**

Toxoplasma gondii is an intracellular parasite that infects birds and mammals. Its definitive host is the cat and other Felidae species. Excretion of oocytes in its faecal content followed by human contaminated uncooked consumption can lead to human infection. In immunocompetent individuals, it primarily causes a subclinical or asymptomatic infection. In immunocompromised individuals (e.g. AIDS patients), toxoplasmosis is the most common cause of a brain abscess.

Pathologically, parenchymal toxoplasma lesions have three distinct zones:

•a central avascular zone of coagulative necrosis

•an intermediate vascular zone containing numerous organisms

•an outermost zone of encysted organisms: Toxoplasma lesions do not have capsule.

**Radiographic features:**

Typically cerebral toxoplasmosis manifest as multiple lesions, with a predilection for the basal ganglia, thalami, and corticomedullary junction.

**Computed tomography (CT):**

Typically, cerebral toxoplasmosis appears as multiple hypodense regions predominantly in the basal ganglia and at the corticomedullary junction. However, they may be seen in the posterior fossa. Size is variable, from less than 1 cm to more than 3 cm, and there may be associated mass effect.

•enhancement: following administration of contrast there is nodular or ring enhancement which is typically thin and smooth.

•double-dose delayed scan: may show a central filling on delayed scans

•calcification: seen in treated cases; may be dot-like or thick and 'chunky'

**Treatment and prognosis:**

In general, biopsy is not required and treatment is initiated and follow-up imaging performed. The exception to this rule are patients who have atypical imaging features (e.g. single lesion) or who are seronegative for Toxoplasma gondii.

Treatment consists of sulfadiazine with pyrimethamine. [(7)]

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# African Trypanosomiasis

Human African trypanosomiasis, also known as sleeping sickness, is a vector-borne parasitic disease. It is caused by infection with protozoan parasites belonging to the genus Trypanosoma. They are transmitted to humans by tsetse fly (Glossina genus) bites which have acquired their infection from human beings or from animals harbouring human pathogenic parasites.

Tsetse flies are found just in sub-Saharan Africa though only certain species transmit the disease. For reasons that are so far unexplained, in many regions where tsetse flies are found, sleeping sickness is not. Rural populations living in regions where transmission occurs and which depend on agriculture, fishing, animal husbandry or hunting are the most exposed to the tsetse fly and therefore to the disease. The disease develops in areas ranging from a single village to an entire region. Within an infected area, the intensity of the disease can vary from one village to the next.

## Forms of human African trypanosomiasis

Human African trypanosomiasis takes 2 forms, depending on the parasite involved:

Trypanosoma brucei gambiense is found in 24 countries in west and central Africa. This form currently accounts for 97% of reported cases of sleeping sickness and causes a chronic infection. A person can be infected for months or even years without major signs or symptoms of the disease. When more evident symptoms emerge, the patient is often already in an advanced disease stage where the central nervous system is affected.

Trypanosoma brucei rhodesiense is found in 13 countries in eastern and southern Africa. Nowadays, this form represents under 3% of reported cases and causes an acute infection. First signs and symptoms are observed a few months or weeks after infection. The disease develops rapidly and invades the central nervous system. Only Uganda presents both forms of the disease, but in separate zones.

Another form of trypanosomiasis occurs mainly in Latin America. It is known as American trypanosomiasis or Chagas disease. The causal organism belongs to a different Trypanosoma subgenus and is transmitted by different vector. [(9)]

## Clinical features:

### Early (hemolymphatic) stage:

The onset is variable but usually occurs 1–3 weeks after the bite. Episodes of fever lasting 1–7 days occur together with generalized lymphadenopathy. The early symptoms tend to be non-specific: malaise, headache, arthralgia, generalized weakness, and weight loss. Multiple organs may then be infected, including the spleen, liver, skin, cardiovascular system, endocrine system, and eyes. This involvement underlies the wide spectrum of systemic dysfunction that may occur.

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**Late (encephalitic) stage:**

The onset is insidious and the potential clinical phenotype is wide. The broad neurologic spectrum has been detailed elsewhere, and the reported features can be grouped into general categories such as psychiatric, motor, and sensory abnormalities, and sleep disturbances. The mental disturbances may be subtle, and include irritability, lassitude, headache, apparent personality changes, and overt psychiatric presentations such as violence, hallucinations, suicidal tendencies, and mania. Motor system involvement may include limb tremors, tongue and limb muscle fasciculation, limb hypertonia and pyramidal weakness, choreiform and athetoid movements, dysarthria, cerebellar ataxia, and polyneuritis. Pout and palmar-mental reflexes may also be present. Sensory involvement may manifest as painful hyperaesthesia, pruritis, and also deep hyperaesthesia (Kerandel's sign), the latter being reported as particularly common in Europeans. The characteristic sleep disturbances include lassitude, distractibility, and spontaneous, uncontrollable urges to sleep, along with a reversal of the normal sleep-wake cycle in which daytime somnolence alternates with nocturnal insomnia. While these various features, including the sleep abnormalities, are typical of HAT, they are not individually diagnostic, since some of them may also be seen during other CNS infections. If untreated, the patient progresses to the final stage of the disease, which is characterized by seizures, severe somnolence, double incontinence, cerebral edema, coma, systemic organ failure, and inevitable death.

**Diagnosis:**

The diagnosis of HAT is based on a combination of clinical and investigative data. A typical clinical presentation in the context of a geographical location where HAT is known to be endemic is clearly the key diagnostic clue. However, the non-specific nature of many of the clinical features makes it imperative to exclude other infections such as malaria, tuberculosis, HIV infection, leishmaniasis, toxoplasmosis, hookworm infection, typhoid, and viral encephalitis. A particular pitfall is that inappropriate antimalarial treatment may actually reduce the fever due to HAT, thus confounding and delaying the correct diagnosis, and these two conditions may also co-exist.

Specific diagnosis at the hemolymphatic stage ideally involves demonstration of the trypanosomes in the peripheral blood using stained thick and thin films, or in other infected tissues such as lymph node aspirates or occasionally bone marrow. While parasite detection in the blood is frequently successful in rhodesiense infection because of the permanent parasitaemia, this method is very difficult in gambiense infection, in which few parasites are present in the peripheral circulation other than at periods of cyclic parasitaemia, which reflects the chronicity of the disease. Therefore, serologic tests are of crucial importance in the diagnosis of gambiense infection. Currently the antibody-detecting card agglutination trypanosomiasis test (CATT) is in frequent use for serological gambiense diagnosis, being simple, easy to perform, and rapid.

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The key issue in HAT diagnosis and therapeutic decision making is to distinguish reliably the late encephalitic stage of HAT from the early stage. Accurate staging of HAT is critical because failure to treat a patient with CNS involvement will lead inevitably to death from the disease, yet inappropriate CNS treatment in an early-stage patient carries a high risk of unnecessary drug toxicity (see below). In patients with suspected late-stage disease it is imperative to perform a lumbar puncture, which typically shows a lymphocytic pleiocytosis and raised protein level of 40–200 mg/100 ml. Further, all CATT-positive patients also need to undergo a lumbar puncture, as there are no reliable clinical suspicion criteria for early-stage disease. The WHO criteria for CNS involvement, and therefore for CNS drug treatment, are demonstration of the parasites in the CSF or a white blood cell (WBC) count of >5/μl. However, these criteria have been challenged by some investigators. Thus, in Angola and the Ivory Coast the criterion used for CNS involvement is 20 WBCs/μl in the CSF. It has also been pointed out that concentration techniques for trypanosome detection in the CSF vary, and that a CSF pleiocytosis may be non-specific. Recently it has been shown that detection of intrathecal IgM synthesis is a very sensitive marker for CNS involvement in sleeping sickness. The latex agglutination assay for CSF IgM quantitation can be applied in the field and has considerable promise for both staging CNS sleeping sickness and monitoring the development of treatment relapses.

CSF PCR to detect trypanosome DNA has also been used in the diagnosis of HAT, but considerable care must be used in the correct choice of primers, and problems with assay reproducibility have been documented. It has recently been reported that CSF PCR has a sensitivity rate of 96%, although its value for therapeutic decision making has been questioned. Therefore, PCR has not yet superseded serological diagnosis and, crucially, it is not readily available in field conditions. It has recently been suggested by Lejon et al. that the WHO criteria should be replaced by the presence of intrathecal IgM synthesis or the presence of >20 WBCs/μl, independent of the presence of trypanosomes in the CSF. This author regards the presence of trypanosomes in the CSF as compelling evidence of CNS involvement. However, patients with gambiense disease who have trypanosomes in the CSF and <20 WBCs/μl have been treated successfully with pentamidine, so perhaps one might speculate that there is a kind of ‘intermediate stage’ in which the trypanosomes can cross the blood-brain barrier without invading and damaging brain structures at that stage. Thus there are two critical, and not necessarily congruent, issues involved, one being the biological definition of CNS involvement, and the other being the ground for therapeutic choices. This lack of a universal consensus on the operational definition of late-stage HAT remains very problematic, but the clear requirement is to develop robust surrogate markers to guide therapeutic choices. These diagnostics need to be novel, simple, and affordable.

Electroencephalogram (EEG) and sophisticated neuroimaging are limited to specialist centers, but both have shown abnormalities in HAT. During the encephalitis stage the EEG shows non-specific abnormalities, which correlate with the severity of the disease. Changes include at least three different types of abnormal EEG patterns, which become normal after clinical improvement. Abnormalities reported on computed tomography scans and MRI are non-specific and not pathognomonic, but if available these tests should be carried out, partly to monitor the response to treatment, and also where the diagnosis is in doubt or where raised intracranial

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pressure is present. MRI of the brain may show diffuse asymmetric white matter abnormalities, diffuse hyperintensities in the basal ganglia, and ventricular enlargement.

**Neuropathogenesis:**

The pathologic substrate of late-stage sleeping sickness is a meningoencephalitis in which cellular proliferation occurs in the leptomeninges, and a diffuse perivascular white matter infiltration consisting of lymphocytes, plasma cells, and macrophages is prominent. The perivascular cuffs and adjacent parenchyma contain markedly activated astrocytes and macrophages, and the white matter contains pathognomonic morular or Mott cells, which are thought to be modified plasma cells containing eosinophilic inclusions comprising IgM.

Current understanding of the highly complex pathogenesis of sleeping sickness is based mainly on studies carried out either on patients' blood and CSF samples or in experimental animal models. In both cases, correlation of specific clinical features or stages with alterations of different biochemical or immunological parameters has often yielded interesting results, but caution must be used in assuming a cause-and-effect relationship between the investigation and the disease phenotype. Care must also be used in extrapolating results obtained in animal models to the human disease.

Alteration of cytokine levels has been detected in patients with CNS sleeping sickness. For example, significant elevations of IL-10 were detected in both the plasma and CSF in both early- and late-stage rhodesiense disease, and declined after treatment to the levels found in uninfected control persons. Total, but not free, plasma TNF-α levels were also higher in late-stage disease compared with levels obtained after treatment. However, the source of IL-10 elevation is unclear. Similar studies in patients with gambiense infection have also reported elevations of CSF IL-10 levels in late-stage disease, as well as a rise in IL-6 and IL-8. Other abnormalities which have been reported in patients with CNS HAT include much raised CSF levels of prostaglandin D2, which may be related to the marked somnolence, and raised blood and CSF endotoxin levels that may also contribute to the CNS pathology.

Several possible causes of PTRE have been suggested, including subcurative chemotherapy, abnormal immune responses to glial cell–attached antigens released from killed parasites following melarsoprol treatment, immune complex deposition, arsenical toxicity, and autoimmune mechanisms. PTRE has been studied in a reproducible mouse model that mirrors many of the pathologic features of the disease in humans. Injection of Trypanosoma brucei into mice via the intraperitoneal route leads to a chronic infection in which the parasites are detectable in the CNS after 21 days. If the drug berenil (diminazene aceturate), which does not cross the blood-brain barrier and therefore clears the parasites from the extravascular compartment but not the CNS, is given 21–28 days after infection, the mice develop a severe post-treatment meningoencephalitis, which persists after the parasitemic phase is over. This condition shows strong pathologic similarity to PTRE in humans. A consistent observation in this model is that astrocytes are activated 14–21 days after infection and prior to the development of the inflammatory response, and that transcripts for several cytokines such as TNF-α, IL-1,

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IL-4, IL-6 and IFN-γ can be detected in the brain at this time. Early astrocyte activation is therefore likely to be of central importance in generating the CNS inflammatory response.

Different types of drug have been shown to modulate the inflammatory response in this mouse model. The trypanostatic drug DFMO has the ability to prevent the development of PTRE or ameliorate it once it is established in terms of greatly reducing both the neuropathology and the degree of astrocyte activation. The immunosuppressant drug azathiaprine can prevent but not cure PTRE, and the non-peptide Substance P (SP) antagonist RP-67,580 has been shown to significantly ameliorate both the neuroinflammatory reaction and the level of astrocyte activation. Although this showed that SP plays a role in generating the inflammatory response in this PTRE, recent evidence has shown that this is complex, since infected SP knockout mice show a novel phenotype in which the clinical and neuroinflammatory responses were dissociated with evidence of alternative tachykinin receptor usage. There is also evidence for the role of various chemokines such as macrophage inflammatory protein (MIP)-2, RANTES, and MIP-1α produced by astrocytes, microglia, and T cells early in the CNS infection in a rat model. It should also be pointed out that in both human disease and animal models the cellular sources of these cytokines and neuropeptides are sometimes not known and are only inferred, with multiple stimuli for their secretion likely.

It is clear that macrophage activation by both parasite components and host-derived cytokines is central to HAT pathogenesis. Both VSG and GPI anchors are known to be potent macrophage activators, as is IFN-γ, which itself may derive from several sources, including CD4+ and NK cells. A molecule called trypanosome-derived lymphocyte triggering factor has been described in mouse and rat models. This molecule triggers the CD8+ T cell to produce IFN-γ, which both activates macrophages and apparently has growth-enhancing effects on trypanosomes. The overall picture that is now emerging is a highly complex network of cytokine-brain interactions, with early astrocyte activation, macrophage activation, and, at least in animal models, an inflammatory cytokine response being prominent features.

**Treatment:**

The current treatment of HAT is based on four main drugs, namely suramin, pentamidine, melarsoprol, and eflornithine (difluoromethylornithine, or DFMO), with nifurtimox undergoing evaluation. [(10)]

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## Cerebral malaria

Malaria is the most important of the parasitic diseases of humans, and its neurological complication, cerebral malaria is arguably one of the most common non-traumatic encephalopathies in the world. Malaria affects about 5% of the world's population at any time and causes somewhere between 0.5 and 2.5 million deaths each year. There are four species of human malaria, but Plasmodium falciparum causes nearly all the deaths and neurological complications. Severe malaria occurs predominantly in patients with little or no background immunity—that is, children growing up in endemic areas, or travelers or migrants who come from areas without malaria, but are exposed to malaria later in life. The manifestations of severe malaria differ depending on the age of the patient and previous exposure. In the first 2 years of life severe anaemia is a common presenting feature of severe malaria. In older children seizures and cerebral malaria predominate; whereas in adults acute renal failure, acute pulmonary oedema, liver dysfunction, and cerebral malaria may all occur. Metabolic acidosis, mainly a lactic acidosis, is common at all ages. Severe malaria is a multisystem disease, and the outcome often depends on the degree of vital organ dysfunction.

P falciparum is transmitted by female Anopheles mosquitoes. In humans, although the parasite undergoes development in the liver, it is the erythrocytic cycle that is responsible for disease. The merozoites released by the liver invade the erythrocyte, and during a period of 48 hours, pass through morphologically distinct stages, before the meronts (schizonts) rupture the erythrocyte. Ring stages are seen in the peripheral blood, but trophozoites and meronts are usually absent, as they are sequestered within the deep vascular beds.

### Definition of cerebral malaria:

The term “cerebral malaria” has often been used loosely in the medical literature to describe any disturbance of the CNS in a malaria infection. In the case reports of the cerebral involvement caused by P.vivax, other causes of an encephalopathy or mixed infections with P falciparum have not been adequately excluded. In falciparum malaria, disturbances of consciousness can be caused by systemic complications—for example, fever, hypoglycaemia, hypernatremia, and uremia. To allow comparison between patient populations in different countries, a strict definition of cerebral malaria was suggested: defined as a deep level of unconsciousness (inability to localise a painful stimulus) in the presence of a P falciparum asexual parasitaemia, after the correction of hypoglycaemia and exclusion of other encephalopathies, especially bacterial meningitis and locally prevalent viral encephalitides. In adults, coma was required for more than 6 hours after a generalised convulsion to exclude a transient postictal state (which rarely lasts more than 1 hour), although in children this was reduced to 1 hour. In fatal cases, the diagnosis of cerebral malaria is supported by finding cerebral capillaries and venules packed with PRBCs. These features may be absent if the patient dies after several days of treatment, and are not specific for cerebral malaria. In clinical practice, any impairment of consciousness or other sign of cerebral dysfunction is an indication for parenteral treatment and intensive care management.

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**Pathological features of cerebral malaria:**

The histopathological hallmark of cerebral malaria is engorgement of cerebral capillaries and venules with parasitised red blood cells (PRBCs) and non-paratised RBCs (NPRBCs).The brain is usually swollen at postmortem, although evidence of frank herniation is unusual in adults. The cut brain is slate grey, with petechial haemorrhages. The endothelium does not demonstrate microscopical damage, but immunohistochemical staining suggests endothelial activation3 and disruption of the blood-brain barrier. Inflammatory cells and immune complex deposition are not consistent features in necropsy series to date although some authors think that cerebral malaria has features of a diffuse encephalomyelitis.

**Sequestration:**

The sequestration of red cells containing mature forms of the parasite (trophozoites and meronts) in the microvasculature is thought to cause the major complications of falciparum malaria, particularly cerebral malaria. This process varies considerably between organs (the brain is particularly affected) and at a microvascular level varies between vessels. The sequestration of PRBCs in the relatively hypoxic venous beds allows optimal parasite growth and prevents the PRBCs from being destroyed by the spleen. It is the sequestered parasites that cause pathology in severe malaria, and prognosis is related to sequestered biomass. The peripheral blood parasite count is a relatively poor predictor of the size of this biomass. In a recent postmortem study of fatal falciparum malaria in adults, the median ratio of cerebral to peripheral blood parasitaemia was 40 (range 1.8–1500).In this study, although most sequestered parasites were the mature stages not seen in the peripheral blood, there were considerably more ring stages than expected from a free mixing model. Patients who have died from non-neurological complications of falciparum malaria also show cerebral sequestration at necropsy, although the intensity is less in patients who die without preceding coma. Many authors have commented on the lack of correlation between the necropsy findings and clinical features of cerebral malaria; although one study showed a correlation between the degree of PRBC sequestration and depth of coma on admission. Some authors have suggested that cerebral malaria may occur in the absence of cerebral sequestration. These discrepancies can be explained by the variable interval between starting antimalarial treatment and death; fatal cases without cerebral sequestration have invariably received many days of antimalarial treatment before dying.

**Cytoadherence:**

Sequestration is thought to be a specific interaction between PRBCs and the vascular endothelium (cytoadherence). This phenomenon seems to be mediated by plasmodium derived proteins on the surface of PRBCs and modified erythrocyte cell wall proteins and ligands on endothelial cells. The adhesion of the PRBCs reduces the microvascular blood flow, which may explain organ and tissue dysfunction such as coma. The metabolically active sequestered parasites may compete with host tissues for substrates—for instance, glucose—and also produce toxins that interfere with host tissue metabolism. Unfortunately, there is no satisfactory animal model of human cerebral malaria. In vitro models show that cytoadherence begins when the parasites produce visible malaria pigment (usually becoming visible under light microscopy

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around 16 hours), which is maximal at the late stages. Cytoadherence occurs predominately in capillaries and venules, as it is overcome by large shear stresses encountered on the arterial side. Freshly isolated PRBCs capable of cytoadherence have electron dense “knobs” protruding from their surfaces, composed of proteins derived from the parasite, notably the adhesin P falciparum erythrocyte membrane protein-1 (PfEMP-1). This family of large proteins (200–350 kDa) which are expressed on the exterior of PRBCs vary antigenically with time in cloned parasites. This programmed variation allows the parasites to evade host immune responses. These proteins have adhesive properties and are primarily responsible for cytoadherence. A family of more than 150 highly variable (“var”) genes encode PfEMP-1, which can bind to several candidate endothelial receptors. Some of these vascular receptors, such as the main candidate CD36, seem to be expressed at all times in a wide range of vascular beds and are regarded as constitutive; their expression is not related qualitatively or quantitatively to severity of disease. Other receptors such as intracellular adhesion molecule-1 (ICAM-1) and endothelial selectin (E-selectin) are inducible, with increased expression in the cerebral vessels of patients with cerebral malaria, which co-localises with sequestration, suggesting that they may be responsible for cytoadherence. Monoclonal antibodies against ICAM-1 improve microcirculatory flow in ex vivo models of malaria sequestration, but have not been evaluated in humans. The process of PRBC cytoadherence has several parallels to that of leucocyte adherence to the vascular endothelium. Firstly, rolling occurs along the endothelial surface, followed by static adherence, which reduces flow in packed partially obstructed vessels.

The clinical correlates of these in vitro models are poor. Parasitised red blood cells from Gambian children with cerebral malaria did not bind more avidly to C32 melanoma cells than isolates from children with less severe disease. Although binding to CD3619 has been shown to be directly proportional to parasitaemia, the degree of binding to CD36 cells correlated with biochemical indicators of disease severity in adult Thai with malaria, rather than coma. In adults with cerebral malaria there was an increase in vessels expressing ICAM-1 and E-selectin, but not other ligands; whereas in Kenyan children, there was a relation between cerebral malaria and binding to CD36, ICAM-121 and a mutation in the ICAM-1, although this was not confirmed in other sites in Africa. Studies on peripheral blood parasites reflect the entire repertoire of adhesins, and may not be representative of cytoadherence in a particular organ.

**Rosetting and agglutination:**

The adherence of NPRBCs to PRBCs (rosetting) and PRBCs to PRBCs (agglutination), have also been implicated in the pathogenesis of cerebral malaria, although most clinical studies have failed to show an association. In rosetting, the var genes seem to be responsible for the ligands and this intererythrocytic interaction is pH and heparin sensitive. It can be disrupted by antibodies to P.falciparum, glycosaminoglycans, sulfated glycoconjugates in a strain and isolate specific manner. Rosettes are disrupted at high flow rates, although they reform at lower shear stresses, aggravating the venular obstruction in a rodent ex vivo model of sequestration. Increased rosette formation was found in Gambian children with cerebral malaria, with a corresponding lack of antirosetting antibodies, whereas studies from other parts of the world did

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not show such an association. The contribution of agglutination to the pathophysiology of severe malaria is unclear.

**Red cell deformability:**

As the parasite grows within the RBCs, the erythrocyte becomes less deformable, which may contribute to the RBC destruction and impair the microcirculatory flow. The reduction in red cell deformability not only occurs in PRBCs, but also the NPRBCs. The NPRBCs have to undergo considerable deformation as they squeeze through the sequestered microcirculation. Microvascular perfusion in severe falciparum malaria is therefore limited by mechanical obstruction, adherence of other RBCs, and the stiffness of the non-adherent RBCs. Red cell deformity measured at low shear rates encountered in capillaries and venules, proved the most powerful prognostic indicator of severe malaria in a study of Thai adults, although not associated with the syndrome of cerebral malaria itself. Similar studies in Kenyan children also showed a strong association with severe disease and a predictable increase in red cell deformity with blood transfusions.

**Cytokines:**

Blood concentrations of proinflammatory cytokines are raised in cerebral malaria, as in many severe infections. Tumour necrosis factor-α (TNF-α) upregulates endothelial cytoadherence receptors and can cause hypoglycaemia and dyserythropoiesis, which are features of severe disease.

In African children, high concentrations of TNF-α are associated with coma, hypoglycaemia, hyperparasitaemia, and death. Early studies suggested that increases in proinflammatory cytokine concentrations were associated with cerebral malaria, generating the hypotheses that cytokines produced coma. Thus Clarkeet al suggest that TNF-α induces the release of nitric oxide (NO), which interferes with synaptic transmission, causing coma. More recent studies in adults indicate that the increases in cytokine concentration relate more to overall severity. Plasma concentrations of TNF-α, interleukin (IL)-6, and IL-10 were higher in Vietnamese adults who died with severe malaria than survivors; but these increases were not associated with cerebral malaria. Indeed, concentrations of proinflammatory cytokines were significantly lower in patients with pure cerebral malaria than in those with multiple organ dysfunction. Fatal malaria is associated with a relative deficiency of IL-10 production, an anti-inflammatory cytokine that controls the production of the proinflammatory cytokines. Persuasive evidence for a role of proinflammatory cytokines in lethal malaria comes from the finding that Gambian children homozygous for the 308 TNF promoter polymorphism allele are at a significantly increased risk of dying of cerebral malaria.

However, there are inconsistencies. In patients with severe malaria, the blood concentrations of TNF-α receptors are markedly increased and bioactive TNF-α is seldom detectable. There is considerable overlap between the distribution of cytokine concentrations in the different clinical patterns of malaria.34 Concentrations of TNF-α measured in paroxysms of uncomplicated P vivax infections are as high as those measured in patients with cerebral malaria, but this infection rarely causes neurological disturbances. The administration of monoclonal anti-TNF, reduced

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temperature, indicating bioactivity against pyrogenic cytokines, but did not affect outcome. Plasma concentrations of nitrate and nitrite (so called reactive nitrogen intermediates (RNI)), surrogate measures for NO, have been shown to be raised in some series but low in others. The RNIs are crude measures of NO production, as they are also influenced markedly by diet, and their elimination is via the kidney. In Papua New Guinea, these metabolites were highest in children with cerebral malaria, particularly those who died. In African children, NO production was lowest in those aged 1–5 years, the age at which children are most susceptible to cerebral malaria. The metabolites are lower in plasma of children admitted with cerebral malaria, but higher in the CSF of children who died in one study, but not in another. In Vietnamese and Thai adults the increase in plasma concentration of RNI in severe malaria (particularly fatal cases) was accounted for entirely by renal impairment, and thus reduced RNI clearance rather than cerebral involvement. Therefore, if cytokines and NO have an important pathogenic role, it is likely to be at the local tissue level, rather than systemically.

**Cerebral malaria in adults:**

**Clinical features:**

Cerebral malaria is a diffuse encephalopathy in which focal neurological signs are relatively unusual. The patient is febrile and unconscious with divergent gaze and variable tone. There may be passive resistance to neck flexion, but of a lesser degree to the “meningism” associated with meningitis. There is no rash, and no lymphadenopathy. As cerebral malaria is often accompanied by multisystem dysfunction, an assessment of the degree of anaemia, jaundice and, most importantly, the presence of acidotic (Kussmaul's) breathing is important. The prognosis of cerebral malaria worsens considerably with coexistent renal failure, severe jaundice, or metabolic acidosis. The metabolic acidosis is caused by either an acute renal failure, or a lactic acidosis, or a combination of both. Acute pulmonary oedema may occur. Rarely, patients with severe malaria have disseminated intravascular coagulation and evidence of bleeding, usually from the upper gastrointestinal tract but sometimes in the skin. The pulse is usually rapid and full, with a low or normal blood pressure. The peripheries are well perfused, although shock may occur and is often terminal. Hypoglycaemia (plasma glucose<2.2 mmol/l) is common in severe malaria, occurring in about 8% of adults and about 20% of children with cerebral malaria. It is usually not accompanied by noticeable sweating or gooseflesh or other physical signs of hypoglycaemia. All patients with severe malaria should have frequent checks of blood glucose. Restoration of normoglycaemia, however, is often not associated with a change in the level of consciousness.

On direct ophthalmoscopy retinal haemorrhages are found in about 15% of patients. These are boat or flame shaped and sometimes resemble Roth spots with a pale centre. They usually spare the maculae. Indirect ophthalmoscopy discloses haemorrhages in a much higher proportion of patients. These haemorrhages seldom involve the macula. Areas of unusual retinal “whitening” may also be seen and occasional cotton wool spots. Papilloedema is very unusual in adults. The pupillary reactions are usually normal and the range of eye movements full, although gaze is

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dysconjugate. Sixth nerve palsies may occur rarely. The corneal reflexes are usually present although in very deep coma they may be lost. The remainder of the cranial nerve examination is usually normal. A pout reflex may sometimes be elicited and bruxism is common but other "frontal release" signs are unusual. Stereotyped movements, commonly seen in encephalitides, are not seen in cerebral malaria. Tone and reflexes are variable. The abdominal reflexes are almost always absent, the plantars often upgoing, and ankle and patellar clonus can sometimes be elicited in hypertonic patients.

**Seizures**:

The incidence of convulsions in adults with cerebral malaria varies. In the early 1980s studies conducted in Thailand and Vietnam, 50% of adults with cerebral malaria had generalised seizures, whereas in these countries in the 1990s the incidence was less than 10%. The reason for this difference is not clear. Possible explanations include differences in parasite virulence characteristics, or possibly the decrease in the use of chloroquine pretreatment. Partial motor seizures may also occur and in occasional cases the evidence for seizure activity is subtle, such as repetitive eye or hand movements, and may be easily overlooked. Subtle evidence for seizure activity seems to be more common in children than in adults. The level of consciousness after a seizure is usually lower than that preceding it. Status epilepticus is unusual in adults, although more than one seizure is common.

**Outcome:**

The overall mortality of adult cerebral malaria is about 20%.52 Mortality depends on the associated vital organ dysfunction. In patients with "pure" cerebral malaria and no other evidence of vital organ dysfunction the mortality is 8%, whereas it rises towards 50% with associated acute renal failure and metabolic acidosis. Mortality is also dependent on the availability of intensive care facilities. If the patient can be ventilated if needed and renal replacement therapy (preferably haemofiltration) provided, and there is careful nursing of the unconscious patient, then mortality is reduced. The patient may die from a sudden acute respiratory arrest, often after a period of respiratory irregularity, but with a normal blood pressure. Other patients may die from shock and others from hypoxia and hypotension secondary to acute pulmonary oedema or sometimes aspiration pneumonia. Most deaths occur within 48 hours of admission. Full recovery of consciousness takes a median of 2 days in patients with a summated Glasgow coma score <11 but occasional adult patients may take more than 1 week to recover consciousness.

**Cerebral malaria in children:**

In African children growing up in malarious endemic areas, severe falciparum malaria usually manifests as seizures, impaired consciousness, or metabolic acidosis presenting as respiratory distress or severe anaemia. Compared with adults, children have a higher incidence of seizures;

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the incidence and pattern of neurological Sequelae are different and they often die with features of brain death. African children rarely develop renal failure or pulmonary oedema.

In older children, cerebral malaria can be defined as in adults. The Blantyre coma scale, was devised to assess young children with severe malaria and a summated score⩽2 is used to define cerebral malaria in many studies. The Blantyre coma scale has similar components to the Glasgow coma scale, but measures different responses. However, there is considerable disagreement between observers in assessing the scale, and the scale does not address the inability of young infants to localise a painful stimulus. [(11)]

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## Naegleria fowleri infection

Naegleria fowleri (commonly referred to as the “brain-eating amoeba” or “brain-eating ameba”), is a free-living microscopic ameba*, (single-celled living organism). It can cause a rare and devastating infection of the brain called primary amebic meningoencephalitis (PAM). The ameba is commonly found in warm freshwater (e.g. lakes, rivers, and hot springs) and soil. Naegleria fowleri usually infects people when contaminated water enters the body through the nose. Once the ameba enters the nose, it travels to the brain where it causes PAM, which is usually fatal. Infection typically occurs when people go swimming or diving in warm freshwater places, like lakes and rivers. In very rare instances, Naegleria infections may also occur when contaminated water from other sources (such as inadequately chlorinated swimming pool water or heated and contaminated tap water) enters the nose 1-4. You cannot get infected from swallowing water contaminated with Naegleria. [12]

**History:**

The first PAM infections were reported in 1965 in Australia. The ameba identified caused a fatal infection in 1961 and turned out to be a new species that has since been named Naegleria fowleri after one of the original authors of the report, M. Fowler. The first infections in the U.S., which occurred in 1962 in Florida 2, were reported soon after. Subsequent investigations in Virginia using archived autopsy tissue samples identified PAM infections that had occurred in Virginia as early as 1937.

**Pathogen & Environment:**

Naegleria fowleri is a heat-loving (thermophilic), free-living ameba (single-celled microbe), commonly found around the world in warm fresh water (like lakes, rivers, and hot springs) and soil. Naegleria fowleri is the only species of Naegleria known to infect people. Most of the time, Naegleria fowleri lives in freshwater habitats by feeding on bacteria. However, in rare instances, the ameba can infect humans by entering the nose during water-related activities. Once in the nose, the ameba travels to the brain and causes a severe brain infection called primary amebic meningoencephalitis (PAM), which is usually fatal. [13]

**Illness & Symptoms:**

Primary amebic meningoencephalitis (PAM), is a disease of the central nervous system. PAM is caused by Naegleria fowleri, a free-living ameba. It is a rare disease* that is almost always fatal; only 4 people in the U.S. out of 143 have survived infection from 1962 to 2016 4. Signs and symptoms of Naegleria fowleri infection are clinically similar to bacterial meningitis, which lowers the chances of initially diagnosing PAM . Humans become infected when water containing Naegleria fowleri enters the nose and the ameba migrates to the brain along the olfactory nerve. People do not become infected from drinking contaminated water. Symptoms start 1-9 days (median 5 days) after swimming or other nasal exposure to Naegleria-containing water. People die 1-18 days (median 5 days) after symptoms begin. PAM is difficult to detect

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because the disease progresses rapidly so that diagnosis is usually made after death. Signs and symptoms of the infection include:

**Stage 1:**

•Severe frontal headache

•Fever

•Nausea

•Vomiting

**Stage 2:**

•Stiff neck

•Seizures

•Altered mental status

•Hallucinations

•Coma. [14]

**Diagnosis & Detection:**

Primary amebic meningoencephalitis (PAM) is a serious infection and inflammation of the brain caused by Naegleria fowleri. The disease is diagnosed using specific laboratory tests available in only a few laboratories in the United States. Because of the rarity of the infection and difficulty in initial detection, about 75% of diagnoses are made after the death of the patient.

PAM and Naegleria fowleri infection can be diagnosed in the laboratory by detecting:

• Naegleria fowleri organisms in cerebrospinal fluid (CSF), biopsy, or tissue specimens, or

• Naegleria fowleri nucleic acid in CSF, biopsy, or tissue specimens, or

• Naegleria fowleri antigen in CSF, biopsy, or tissue specimens.

**Test methods:**

The motile amebae can often be seen moving rapidly under a microscope when looking at a fresh sample of CSF. The amebae can also be stained with a variety of stains, such as Giemsa-Wright or a modified trichrome stain, for identification. [15]

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## Neurocysticercosis

Cysticercosis (i.e., infection caused by eggs of the pork tapeworm) is an increasingly common medical problem in the United States, especially in the Southwest and other areas where large populations migrated from endemic areas and among populations that often travel to these areas.

Cysticercosis is caused by the metacestode, or larval, stage of Taenia solium, the pork tapeworm. The clinical syndromes caused by T solium are categorized as either cysticercosis (cysts in various tissues including the brain) or taeniasis (intestinal tapeworm infection).

**Neurocysticercosis** refers to CNS infection with T solium. Neurocysticercosis, which is probably the most common parasitic infestation of the CNS, has gained increased recognition in the last two decades because of the development of MRI and CT scanning in the United States and in countries where neuro cysticercosis is endemic.

**Neurocysticercosis** is further divided into parenchymal and extraparenchymal disease. Parenchymal disease is characterized by infection with cysticerci within the brain parenchyma. Extraparenchymal disease develops when cysticerci migrate to the CSF of the ventricles, cisterns, and subarachnoid space or within the eyes or spinal cord.

**Pathophysiology:**

When humans ingest undercooked pork that contains cysticerci of T solium, the scolex evaginates from the cyst and develops into an intestinal tapeworm (taeniasis). The tapeworm grows to a length of up to 10 meters and has hundreds of proglottids. Mature proglottids contain approximately 50,000 eggs each. Free eggs or whole proglottids are released periodically into the stool of the carrier and can survive in the environment for many months.

When pigs ingest the proglottids or eggs, the eggs hatch, penetrate the pigs' intestinal wall, and spread to skeletal muscle, especially the neck, tongue, and trunk. There, the larvae mature into encysted cysticerci over 2-3 months. The cysticerci suppress the host inflammatory response and can survive in tissues for months to years. The life cycle is completed when humans ingest inadequately cooked pork that contains viable cysticerci.

This cycle of cysts in pigs and tapeworms in humans can be broken if a human ingests eggs excreted in the feces of a human carrier of the pork tapeworm. Humans are an accidental host of the larval stage and develop cysticercosis similar to that in pigs. These cysticerci have tropism for neural tissue and migrate to the brain, although they can also be found in skeletal muscle. Thus, cysticercosis is a foodborne infection and can be acquired in the absence of pork consumption.

Humans can be infected with eggs through fecal-oral transmission or possibly through autoinfection. Fecal-oral contamination usually occurs via infected food handlers via ingestion of fruit and vegetables fertilized with contaminated human waste. The eggs are sticky and can often be found under the fingers of tapeworm carriers. Thus, even populations who do not eat pork can develop cysticercosis. The egg-containing feces can contaminate water supplies in endemic

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areas. If the water is used to irrigate fruits and vegetables, eggs are ingested with the contaminated food. Thus, people who have never visited endemic countries can also develop infection.

Cysticerci are able to survive in the human brain by disarming host defenses. The cysticercus secretes prostaglandins and other compounds (paramyosin, taeniastatin, sulfated polysaccharides) that inhibit or divert complement activation and cytokine production, resulting in only minimal host inflammation around the viable cysticercus. In addition, humoral antibodies do not kill the mature metacestode. Taeniastatin and other poorly defined factors may also interfere with lymphocyte proliferation and macrophage function, inhibiting normal cellular immune defenses. The clinical manifestations commonly result when an inflammatory response develops around a degenerating cysticercus after it has died.

Over a period of years, the parasite may lose its ability to control the host defenses. Consequently, an inflammatory response leads to degeneration of the cysticercus. An inflammatory response that occurs in the CNS parenchyma causes seizures typical of parenchymal neurocysticercosis. As the degeneration continues, the parasite becomes encased in a granuloma, which either resolves or leads to scarring and calcification. In rare cases, patients with numerous parenchymal cysticerci develop a diffuse cerebral edema termed cysticercal encephalitis. Pathologically, cysticercal encephalitis may progress to meningoencephalitis, granulomatous meningitis, focal granulomas or abscess, hydrocephalus, ependymitis, or arteritis.

Approximately 10-20% of patients with neurocysticercosis present with extraparenchymal disease, often with concomitant parenchymal disease. Subarachnoid neurocysticercosis may form in the gyri of the cerebral convexities or in the fissures of the brain, especially the sylvian fissures. These forms of neurocysticercosis are associated with parenchymal inflammation and resemble parenchymal disease in manifestations and pathogenesis.

In severe cases, cysticerci in the sylvian fissures may enlarge to several centimeters in diameter and cause mass effects. Cysticerci can form in the ventricles of the brain, where they can cause hydrocephalus by blocking the outflow of CSF. Obstructive hydrocephalus may also be caused by associated ependymitis. If cysticerci form in the basal cisterns, they can cause basilar arachnoiditis. Arachnoiditis may result in communicating hydrocephalus or vasculitis. Involvement of the arteries may lead to lacunar infarctions or, occasionally, large-vessel strokes.

Cysticerci may be located in the spinal subarachnoid space and the spinal cord medulla. Medullary cysticerci may cause cord compression or other symptoms related to their location. Ocular cysticercosis is generally intravitreal or subretinal. Skeletal muscle cysticerci are common but usually cause only minor local symptoms unless they are present in overwhelming numbers. Subcutaneous cysticerci manifest as painless, palpable, cystic lesions. CNS parenchymal cysticerci may be present in patients with suspected extraparenchymal or extra-CNS disease.

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**Epidemiology:**

**United States:**

Approximately 1,000 new cases of cysticercosis are reported annually in the United States. Most occur among Latin American immigrants in locations such as California, Arizona, and Texas. Less frequently, cysticercosis is observed in immigrants from other areas, including India, Asia, and Africa. A small number of cases of cysticercosis develop in people born in the United States who have traveled to areas in which the infection is endemic. These travelers are often the children of immigrants. Locally acquired infection is rare and is associated with contact with a tapeworm carrier. All tapeworm carriers acquire infection from areas of endemic disease.

In a mortality study using data from the National Center for Health Statistics from 1990 to 2002; 62% of patients with cysticercosis had emigrated from Mexico.

**International:**

An estimated 50-100 million people are infected with cysticercosis worldwide. This is probably an underestimate since many infections go undiagnosed. Neurocysticercosis is one of the leading causes of adult-onset seizures worldwide. CT scanning and MRI of the brain have greatly improved the diagnosis of neurocysticercosis.

Areas of endemic disease include Central and South America, India, China, Southeast Asia, and sub-Saharan Africa. Studies in Latin America and India have noted adult-onset seizures in approximately 2% of the population, with as many as half due to neurocysticercosis. In Latin America, the seroprevalence rate ranges from 4.9-24%. In India, the estimated prevalence is similar. Rural China and Korea have lower infection rates. The seroprevalence in certain rural South American communities is as high as 10-25%.

**Mortality/Morbidity:**

Neurocysticercosis is one of the leading causes of adult-onset seizures and is estimated to cause as many as 50% of adult-onset seizure cases in developing countries where T solium is endemic. Neurocysticercosis was found to be responsible for 10% of newly onset seizures in one Los Angeles, California, emergency department. Overall, among patients who presented to emergency departments with newly onset seizure, neurocysticercosis was found to be responsible for 2.1-5.7% of cases.

A total of 221 deaths were attributed to cysticercosis in the United States from 1990-2002.

Although some patients die of status epilepticus in areas with poor access to medical care, mortality due to parenchymal disease is rare. With modern medical and surgical care, mortality due to extraparenchymal disease is also unusual. However, without aggressive surgical management, hydrocephalus is potentially life-threatening. Even with shunting procedures, subarachnoid cysticercosis is associated with a high 10-year fatality rate.

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**Race:**

Immigrants from countries where T solium is endemic are more likely to be infected. While most of these immigrants are Hispanic and some are Asian, prevalence rates appear to be related more to exposure than to genetic predisposition.

**Sex:**

Cysticercal encephalitis, a severe form of cysticercosis, is more common in children and young females. The cause is unknown.

No other sex predisposition has been noted.

**Age:**

Patients with cysticercosis are typically aged 10-40 years. However, cases have been described in every age group. [16]

**Neurocysticercosis Clinical Presentation:**

**History:**

Neurocysticercosis is a pleomorphic disease, although it sometimes produces no clinical manifestation. This pleomorphism is due to variations in the locations of the lesions, the number of parasites, and the host's immune response.

Many patients are asymptomatic; others report vague symptoms such as headache or dizziness. The onset of symptoms is usually subacute to chronic, with the exception of seizures, which present in an acute fashion. Possible symptomatic presentations are briefly reviewed below.

**Epilepsy:**

Epilepsy is the most common presentation (70%) of neurocysticercosis and is also a complication of the disease. Neurocysticercosis is the leading cause of adult-onset epilepsy and is probably one of the most frequent causes of childhood epilepsy in the world.

Seizures secondary to neurocysticercosis may be generalized or partial. Simple and complex partial seizures may be associated with the presence of a single lesion. Generalized seizures are usually tonic-clonic; this is thought to be related to the presence of multiple lesions. However, irritation of focal cortical tissue by one of the lesions most probably leads to focal onset with secondary generalization. Myoclonic seizures also have been described.

**Headache:**

Headaches may be associated with intracranial hypertension and are indicative of hydrocephalus; they may also result from meningitis. Chronic headaches may be associated with nausea and vomiting (simulating migraines).

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**Intracranial hypertension:**

Most often, intracranial hypertension is due to obstruction of cerebrospinal fluid (CSF) circulation caused by basal or ventricular cysticercosis. It may also result from large cysts displacing midline structures, granular ependymitis, arachnoiditis, or the so-called cysticercotic encephalitis caused by the inflammatory response to a massive infestation of cerebral parenchyma with cysticerci. Affected patients may have seizures and deterioration of their mental status, mainly due to the host's inflammatory reaction as an exaggerated response to the massive infestation.

Diplopia may also result from intracranial hypertension or arachnoiditis producing entrapment or compression of cranial nerves III, IV, or VI.

**Strokes:**

Ischemic cerebrovascular complications of neurocysticercosis include lacunar infarcts and large cerebral infarcts due to occlusion or vascular damage. Hemorrhage can also occur and has been reported as a result of rupture of mycotic aneurysms of the basilar artery. Strokes may be responsible for paresis or plegias, involuntary movements, gait disturbances, or paresthesias.

**Neuropsychiatric disturbances:**

Neuropsychiatric dysfunction can range from poor performance on neuropsychologic tests to severe dementia. These symptoms appear to be related more to the presence of intracranial hypertension than to the number or location of parasites in the brain.

**Hydrocephalus:**

Ten to thirty percent of patients with neurocysticercosis develop communicating hydrocephalus due to inflammation and fibrosis of the arachnoid villi or inflammatory reaction to the meninges and subsequent occlusion of the foramina of Luschka and Magendie. Noncommunicating hydrocephalus may be a consequence of intraventricular cysts.

**Presentations of other forms of neurocysticercosis:**

Patients with intrasellar neurocysticercosis present with ophthalmologic and endocrinologic manifestations mimicking those of pituitary tumors.

Spinal neurocysticercosis is rare and may be either intramedullary or extramedullary. The extramedullary form is the most frequent and is responsible of symptoms of spinal dysfunction such as radicular pain, weakness, and paresthesias. Intramedullary presentation may cause paraparesis, sensory deficits with a level, and sphincter disturbances.

**Ocular cysticercosis:**

Occurs most commonly in the subretinal space. Patients may present with ocular pain, decreased visual acuity, visual field defects, or monocular blindness.

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Systemic cysticercosis is most common in the Asian continent. The parasites may be located in the subcutaneous tissue or muscle. Peripheral nerve involvement as well as involvement of the liver or spleen have been reported. [17]

**Diagnosis:**

It focuses on brain imaging and serological tests are mostly used as confirmatory tools. Most cases, however, occur in poor endemic areas, where both kinds of diagnostic tools are poorly available. Development of point of care diagnostic tests is one of the most important priorities for cysticercosis researches today. The ideal point of care test would require detection of viable cysticercosis and hopefully identify cases with severe or progressive forms of neurocysticercosis, leading to referral of the patient for specialized medical attention.

Diagnosis and characterization of human NCC should be based on a brain imaging examination to observe the characteristics of the lesions, accompanied by a serological test result to confirm the etiology. In the best possible scenario, the immunological test should not only be highly sensitive and highly specific for etiological confirmation but also be able to discriminate infections with living parasites from inactive infections, and correlate the characteristics of the infection with parasite load, for patient management and follow-up. A century of serological assay development for Taenia solium cysticercosis has provided some tests which fulfill several of the above requirements, albeit the ideal assay has yet to be developed.

**Antibody Detection Tests for Cysticercosis:**

Early in the twentieth century, the laboratory diagnosis of tissue parasites was limited to non-specific findings of increased white cell counts, strongly valuing the presence of increased eosinophil numbers. The first serological assays for parasitic infections were complement precipitation and fixation techniques. In 1909, Weinberg used complement fixation with cystic fluid from cysticerci to demonstrate specific antibodies in the sera of a group of cysticercotic pigs. This test became known as ‘Weinberg’s reaction’ and was used until a few decades ago. In 1911, Arthur Moses reported the use of an aqueous cysticercal extract to demonstrate the presence of antibodies in the serum of three patients with subcutaneous cysticercosis and in the cerebrospinal fluid (CSF) of a patient with cysticercosis encephalitis, thus demonstrating for the first time, the presence of anti-cysticercal antibodies in CSF.

In the following decades, many attempts to develop better diagnostic tests focused on indirect, antibody detection assays. Antibody detection does not distinguish active from inactive infections, and is not useful to monitor changes over short periods; however, its diagnostic efficacy is much higher than that of antigen detection assays. These indirect assays include indirect hemagglutination, immunoelectrophoresis, double immunediffusion, precipitation, indirect immunofluorescence, and skin reaction, among others, and are comprehensively described in Flisser et al. By 1971, Engvall and Perlmann described the enzyme-linked immunosorbent assay (ELISA) technique. The ELISA is a quite simple technique, is sensitive, quantitative, and can process many samples at the same time, thus it soon became the most frequently used antibody detection assay (ELISA-Ab). It was initially applied in 1978 for the diagnosis of NCC by Arambulo et al. in cases with high suspicion for NCC, reporting better

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sensitivity than the indirect hemagglutination, the test in use at that time. Coker-Vann et al. then applied the ELISA technique to detect T. solium antibodies in epidemiological studies. Many other laboratories adopted the ELISA-Ab with varied sensitivities according to the antigen and serum panels used. It was evident, however, that the ELISA performed better than the previous techniques. Initial assays used crude metacestode antigens. Better results were obtained using cystic fluid as the antigens, but not with membrane or scolex antigens.

Unfortunately, a series of factors affected the diagnostic capacity of these early techniques: the sensitivity and specificity of each technique, the difficulties in defining appropriate reference sera sets, and the use of crude or minimally purified antigens, leading to non-specific reactions mainly with echinococcosis, schistosomiasis, angiostrongyliasis, sparganosis, and fasciolasis. Case definitions and reference serum batteries were greatly improved with the advent of computed tomography (CT) in 1977 and magnetic resonance imaging in 1986. Cases of NCC could then be differentiated in terms of number of lesions, stage, and location (intraparenchymal or extraparenchymal NCC), variables, which strongly influence the host's humoral immune response.

Antigen characterization became then the objective of researchers looking for improved serological tests. One of the more studied antigens was antigen B, described by Flisser et al. in 1980 as the antigen more frequently recognized by sera from NCC-infected patients, producing a strong antibody response. Use of antigen B in an antibody detecting ELISA in serum as well as in CSF, did not demonstrate much advantage over other antigen sources.Grogl et al. in 1985 characterized a series of antigenic proteins from the total metacestode extract as suitable candidates for immunodiagnosis, using for the first time the EITB technique, originally used for immunodiagnosis of schistosomiasis. A series of other antigens were then purified using chromatographic techniques and were reported to perform with high sensitivity in cysticercosis immunodiagnosis.

In 1989, the EITB (also known as western blot or immunoblot) using the LLGP fraction was developed and quickly became the assay of choice for serodiagnosis. The LLGP-EITB combines the specificity of using antigens previously purified by chromatography plus the resolution capacity of polyacrylamide gel electrophoresis with sodium dodecyl sulfate coupled with the sensitivity of enzyme-based immunodetection. Seven antigenic glycoproteins (GP) were isolated from a total metacestode homogenate and then purified using lentil-lectin chromatography, namely GP50, GP42-39, GP24, GP21, GP18, GP14, and GP13, where the numbers referred to their molecular mass in kilodaltons. The presence of any one of the seven antibody bands defines a positive test, with an initial sensitivity and specificity reported to be 98 and 100%, respectively. No cross-reactions were found in 376 sera from 18 heterologous infections.44 further comparative testing demonstrated the superiority of the LLGP-EITB over ELISA for the diagnosis of human and porcine cysticercosis.

Antibody-detecting techniques in general do not have the capacity to distinguish between exposure, inactive infection and active infection, have a low positive predictive value in cases with viable cysticercosis (due to positive antibody reactions in individuals with calcified cysticerci and a high background of seroprevalence in the general population in endemic areas),

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and have low sensitivity in cases with a single brain lesion. Even though the LLGP-EITB is currently considered the test of choice for serodiagnosis of cysticercosis, it has its own drawbacks, which include the source of antigen (the method requires fresh cysts from infected pigs), and is also a complicated procedure. Thus, more recent research efforts have focused on the characterization and synthesis or production of recombinant forms of the seven LLGP diagnostic antigens to produce simpler and more reproducible assays.

Molecular studies showed that the seven LLGP diagnostic antigens comprise three protein families: GP50, T24/T42, and the 8 kDa family. GP50 is the largest of the LLGP antigens. Although no defined cross-reactions have been reported to any of the LLGPs, a 'bogus' band can appear slightly above GP50 and generates a problem of interpretation when reading the strips, even in patients without evidence of exposure to T. solium, thus its presence as a single reactive band should be taken with caution. GP50 and GP39–42 are the more immunodominant antigens, inducing vigorous IgG-response, both are membrane proteins. Studies have demonstrated that GP24 is a monomeric form and GP is a homodimeric form of the same protein. Both have already been produced as recombinants (rGP50 and rT24H) in an eukaryotic expression system, with good diagnostic performances in EITB and in ELISA, as well as in a novel proprietary technique, the Quick ELISA. In general, rT24H performs slightly better than rGP50, but neither antigen alone reaches the sensitivity and specificity of the combined native LLGP set.

The remaining LLGPs, of lower molecular weights, correspond to a complex group of 8 kDa peptides, which can be found alone or in oligomeric structures, which have molecular masses as large as 42 kDa. Similar antigens have been reported in other taeniid cestodes, such as T. hydatigena, T. multiceps, and Echinococcosis granulosus. These small peptides have been described as excretory/secretory (E/S) products and have been associated with immune evasion functions. In some cases, the immunogenic activity of synthetic and native forms correlate well and thus do not seem to depend on secondary structure resulting from post-translational modifications such as a glycosylation; in some cases, there seems to be a component of the immune response that depends on conformational epitopes. The presence of low molecular bands in the LLGP-EITB is rarely seen in absence of reactivity to the higher LLGP antigens and seems to be associated with more severe infections. The use of these smaller 8 kDa LLGP peptides as serodiagnostic tools has been proposed because of their capacity to discriminate between active and inactive infections and their availability as synthetic peptide. TsRS1 and Ts18var1 are two peptides in this family, with reasonable sensitivity and specificity in ELISA, which greatly improve when used in EITB format. They however, show lower diagnostic utility when compared to the native forms to detect single lesion cases. Other diagnostic candidates in the 8 kDa family have been expressed and produced as recombinant proteins including Ts8B1, Ts8B2, and Ts8B3. Among these, the Ts8B2 antigen was better able to discriminate between cases of active and inactive NCC, although some cross-reactions with echinococcosis and schistosomiasis were observed. Splitting the Ts8B2 in smaller synthetic peptides greatly affected the antigen performance. Yang et al. described a 10 kDa antigen from cyst fluid, also belonging to the 8 kDa family, reacting mainly to IgG4 and IgG1.This 10 kDa antigen was also produced in recombinant form and showed a good performance to differentiate active from inactive NCC.

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Other native antigens under research include parasite proteases. In 2005, Baig et al. described a protease from the T. solium metacestode with L-cathepsin activity and able to degrade IgG (suggesting a role in immune evasion).A second similar protease was also identified by a different group soon after. This protease, produced in recombinant form, had antigenic activity recognized by sera from patients with NCC. Two other protease fractions highly abundant in cystic fluid have been isolated and evaluated in ELISA and EITB with promising results, and in dot blot form, with lower sensitivity, albeit higher specificity.

Synthetic peptide production is appealing for its ease of production and inherent reproducibility. However, to date no synthetic peptide has performed at the level of native antigens for diagnostic purposes. A possible alternative is to use more than one synthetic peptide in the same assay, as in the multiantigen print immunoassay, in which several recombinant or synthetic antigens are printed at different positions along a single strip and thus obviating the need for electrophoretic separation. Recombinant proteins perform better than synthetic peptides, most likely because part of the response is directed towards conformational epitopes. Recombinants to several of the seven LLGP described by Tsang et al., have shown better results than related synthetic peptides in EITB as well as in ELISA. A recently reported recombinant protein, Tsolp, promisingly detected all cases, but specimens from only 13 cases were tested.

Other attempts to develop immunodiagnostic tests include the lymphocyte transformation test (LTT) described by Prasad et al., in 2008, who found 94% of sensitivity and 96% of specificity. This assay requires lymphocyte separation, long incubation time, and a radioactive developer. The authors proposed their use in patients with a single brain lesion but further evaluations are still missing. LTT seems to offer a good alternative to evaluate a host’s exposure to a given antigen but will likely not differentiate active from inactive cases because the assay is based on the presence of memory T cells.

Phage display peptide selection was reported as early as in 1999. Almost 10 years later, Hell et al. produced a synthetic peptide against a scolex antigen with this technology. Initial promising results have been reported for two other peptides produced with this technique. As proposed by Esquivel-Velazquez et al., in 2011, new tools like phage display peptide selection, production of synthetic, and recombinant antigens, could permit us to shorten the path to identify specific antigens capable to distinguish not only the stages of the parasite, but also exposure from viable and non-viable infection. In this way, a good alternative to distinguish exposure from infection could be the use of oncospheral antigens, which to date have mostly been used as vaccine candidates. The 8 kDa antigens seem to be promising candidates to distinguish viable from non-viable NCC; however, the sensitivity of these assays needs improving.

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**Advantages and disadvantages of antibody detection in cysticercosis:**

Sound use of serological assays goes beyond the choice of a test and greatly depends on appropriate interpretation of results in the context of a given patient or a given population. Antibody detection with a sensitive and specific assay is the best alternative to diagnose whether somebody has been infected with cysticerci. Antibody detection however does not discriminate between active and inactive infections and thus its clinical utility is restricted to etiological confirmation (although strong antibody reactions suggest severe infections and, unlike total IgG,8 IgG4 detection can be associated with active infection as well as provide a good monitoring marker for cure).

In field conditions, antibody seroprevalence overestimates the actual prevalence of infection because persons with antibodies from exposure and from past infections are also detected. Even more, there is evidence that almost 40% of the positive results in an endemic area are produced by transient antibodies, which become undetectable within 1 year.101 Detection of parasite specific antibodies in asymptomatic individuals has limited clinical use. Antibody prevalence, however, can provide valuable information on exposure to the parasite, transmission dynamics, risk factors, and incidence calculations, thus it should still be considered a tool for control programs.

In summary, a positive antibody test associated with a suggestive brain image strongly supports the diagnosis of NCC, while in endemic regions where no CT or magnetic resonance imaging is available, a positive antibody test should be mainly used to refer patients with neurological symptoms to a more equipped center for imaging diagnosis and etiological case management.

**Appropriate samples for antibody detection:**

Selection of a particular type of sample depends on the available test and antigen. In a study of Sahu et al., serum performed better than CSF when using E/S antigens but there were no differences when using somatic antigens. In general, the evidence suggests that with properly specific assays, serum performs better than CSF for antibody detection. Some authors note that the simultaneous use of both samples can provide important information on the infection status of the patient.

Tests with less specificity and/or less purified antigens give better results with CSF due to the lower frequency of cross-reacting antibodies in CSF. However, a lumbar puncture to obtain CSF is, however, painful and invasive, and poorly accepted by patients. It is important to note that CSF taken from the ventricles (during surgery or through a shunt) or cisterns (cisternal puncture) can differ from samples collected by lumbar puncture in terms of protein concentration. A gradient along the neuroaxis has been described. Also, there may be intrathecally produced antigens in the CSF, particularly during antiparasitic treatment.

Venipuncture is the preferred collection method for clinical laboratory studies; however, blood can be also collected by finger prick on filter paper. This procedure is quite advantageous for sample storage and transport and is quite well accepted by the population and can be of great use

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in field studies or whenever venipuncture is not possible. The LLGP-EITB works well in blood samples eluted from filter paper, with a high agreement with paired serum samples, although some antibody activity is lost along the process. Placing the piece of filter paper in a liquid buffer preserves the amount of recovered antibodies.

Detection of antibodies in other biological fluids has not been extensively explored. Two reports showed low sensitivity in urine. Saliva gave promising results for diagnosis or even for IgG4 monitoring, 100 but no further experiments have been reported. Tears have also been used for diagnosis of ophthalmic cysticercosis (IgA response) with 100% sensitivity and 92% specificity, although this was tested on only a few cases.

**Antigen Detection Tests for Cysticercosis:**

Direct immunodiagnosis (detection of products of the infective agent in the host) has the advantage of demonstrating active infection and in most cases, the antigen levels are associated with the infective burden and thus the severity of the infection, so this type of test can be used to determine therapeutic decisions and guide the prognosis of the patients. Cure is frequently associated with negative antigen results, and on the other hand, relapses, reinfections, or complications result in increases in circulating antigen levels. Unfortunately, in most cases, the sensitivity of antigen detection assays is inferior to that of indirect, antibody-detecting assays.

The initial reports on finding T. solium antigens in the CSF of patients with NCC used ELISA assays with rabbit polyclonal antisera raised against crude cysticercal extracts. Their results were promising, particularly in terms of specificity (likely resulting from the use of CSF instead of serum, as detailed above).As expected, circulating antigen cannot be demonstrated in the CSF of all NCC patients. Also, only a fraction of all antigens present in the cyst fluid can be detected in the patient's CSF. Circulating antigen can also be detected in serum, as initially demonstrated for T. saginata cysticercosis in cattle and later in human samples.

Monoclonal antibody (MoAb)-based antigen detection greatly improved the performance of these assays. The initial tests for T. solium antigen detection originated from assays developed against T. saginata and performed well thanks to an unexpected interspecies cross-reaction. In 1989, Harrison et al. developed a MoAb against a repetitive epitope from excretory/secretory glycoprotein products of the T. saginata metacestode, HP10. In an ELISA format, HP10 detected circulating antigen in cattle with 200 or more live cysts, with levels detectable in cattle serum as early as 4–5 weeks post-infection. No cross-reactions other than the above described with T. solium were reported. The sensitivity of the HP10 ELISA in CSF of confirmed NCC cases was 72%.A similar method was pursued by Brandt et al. in 1992. They found eight MoAbs of IgM isotype, which when used in combination, had a lower detection limit of 88 live cysts in infected cattle, and also were able to detect antigens as late as 5 weeks post-infection. These MoAbs were also directed against repetitive glycoprotein epitopes.135 Further studies generated IgG MoAbs, which improved the antigen assay performance, reaching 92% sensitivity and 98.7% specificity in sera from cysticercosis-infected cattle. They also showed that the target antigen was thermostable. Heat treatment of samples prior to testing gave better results, in particular fewer non-specific reactions.

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MoAbs against T. solium were first described in 1991. The initial report concludes that the antigen detection test performed well for diagnosis of T. solium cysticercosis, but was not 100% sensitive; the test worked better on CSF than on serum, and antigen levels dropped to undetectable levels after successful treatment. Another anti-T. solium MoAb targeted cyst fluid (1F11, IgG1 isotype) and had a diagnostic sensitivity of 82%, mainly missing cases with fewer lesions or only calcifications. This same group also developed MoAb 4F8. A 4F8-based ELISA was used by them to demonstrate that patients with subcutaneous nodules had higher levels of circulating antigen, likely because subcutaneous cysticercosis is found in pInteresting and very promising tools are nanobodies (Nbs), single domain antibodies that are produced in immunized camelids. These molecules are, highly stable and soluble, devoid of light chains, and capable of binding to antigens with high affinity and specificity. Their small size (12–15 kDa) allows detection of hidden epitopes and expression in various microorganisms.Nbs directed against an 8 kDa antigen of the metacestode have been developed and proven specific for T. solium, without cross-reactions with T. hydatigena, T. saginata, T. crassiceps, and Trichinella spiralis . Further work is needed to determine the utility of these reagents for antigen detection in T. solium cysticercosis.atients with higher parasite burdens.

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**Advantages and disadvantages of antigen detection in cysticercosis:**

Currently available antigen capture assays do not reach the same sensitivity and specificity as antibody-detecting assays, so they are not the best option for initial diagnosis of clinical cases. They, however, provide an exceptional tool for clinical management and follow-up of confirmed cases. As described above, the levels of circulating antigen correlate with the severity and type of NCC infection. In intraparenchymal brain cysticercosis, the higher the number of viable cysts, the higher the antigen level, both in humans and in pigs. In cases of extraparenchymal NCC, which carry a poorer prognosis, the levels of antigen are much higher, particularly in patients with basal subarachnoid NCC10,and also correlate with the volume of the lesions except when hydrocephalus is present. Very high antigen levels should thus raise the suspicion of extraparenchymal NCC or massive intraparenchymal NCC. Since the levels of antigen drop quickly in cured NCC patients, serum antigen monitoring is of great help in the follow-up of clinical cases. Detectable levels of circulating antigen do not always correlate with neurological symptoms. A study in India followed 42 antigen-positive individuals for up to 5 years, and none of them developed neurological symptoms associated with NCC.It follows that the isolated finding of circulating antigen without neurological symptoms or compatible neuroimage should not be interpreted as an indication for therapeutic intervention.

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The usefulness of population-based antigen detection surveys is yet unclear. From the available data, the expected proportion of asymptomatic individuals with viable brain cysticerci and thus positive antigen levels should be quite small. Its use would likely be more productive if focused in patients with compatible symptoms such as seizures or intracranial hypertension. In field studies, one would expect to find a higher prevalence of antibody-positive individuals than antigen-positive individuals, since antibody responses occur in non-viable infections and individuals with exposure only, and for an unknown time after resolution. However, population-based studies show discordant results. In a community in Mexico, 1% of all people were positive to circulating antigen versus 4.8% seropositive to antibodies. In Ecuador, 2.25% of 800 participants in a rural community were positive for antigen, while the antibody seroprevalence measured in a subset of 100 randomly selected samples was 40%. On the other hand, a study in South Africa found more antigen-positive than antibody-positive cases, and another study in Burundi found higher prevalence of antibodies in patients with epilepsy than in controls but no differences in the frequencies of antigen-positive cases between these groups.

**Appropriate samples for antigen detection:**

Compared to serum, CSF had better sensitivity (78% versus 68%) and specificity (73% versus 60%) for antigen detection, when MoAbs are used as capture antibodies. Assays using polyclonal rabbit antisera against specific purified antigens did not show differences in serum versus CSF. Also no advantage was demonstrated when using saliva.

Urine samples are easy to collect, non-invasive and thus are easily provided by patients or villagers. Immunodiagnostic tests in urine have been developed for a variety of infectious diseases, including cysticercosis. The initial study found detectable antigen levels in five out of eight confirmed NCC cases, in an agglutination assay using rabbit antisera to a T. solium total metacestode extract. We have found 92% sensitivity in patients with two or more viable cysts, and 62.5% in single lesion cases using the MoAbs described by Van Kerckhoven et al.as well as a strong correlation between serum and urine levels of antigen. Mwape et al. tested paired urine and serum samples collected in Zambia and Ecuador. A very high agreement (90%) was found between samples of the same individual, but lower specificity when urine samples were tested. The Zambian samples had more non-specific reactions. Urine can also be concentrated to take advantage of the large sample volumes, which can be obtained. Lyophilization avoids the need for further refrigeration or freezing and also results in a slight increase in sensitivity. It, however, also decreases specificity by 2–4%. Other concentration methods were less efficient.

**Single-Lesional NCC:**

A single brain-enhancing lesion is a very frequent presentation of NCC in the Indian subcontinent, where it is also a major contributor to seizures in younger patients. In Latin America, the proportion of NCC patients with a single-enhancing lesion varies from 3.5 to 34%, likely reflecting different definitions of a single-enhancing lesion. More importantly, other infections, tumors, vascular lesions, and other etiologies need to be considered in the differential

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diagnosis of single brain lesions and thus serology could be of great help in saving unnecessary invasive procedures or treatments.

In general, all immunodiagnostic tests show low sensitivity for the diagnosis of single-Lesional NCC, even worse when the lesion has entered in an involutive, degenerative process of resolution following antiparasitic treatment or by natural evolution ('single-enhancing lesion' or single cysticercal granuloma'). A proportion of these cases could also correspond to early lesions, caused by cysticerci that resolved soon after infection, before full establishment and thus not provoking a strong immune response. Most seronegative NCC cases in ELISA or in the LLGP-EITB correspond to cases with a single lesion, although the estimates of sensitivity of the assays in this type of NCC vary greatly. Prabhakaran et al. reported an increase in sensitivity following the use of urea to expose the tertiary structure of the antigenic glycoproteins, detecting 46% of previously negative cases in EITB.

**DNA-based Technology:**

The greatest contribution of DNA-based technology has been in the genotyping of the genus Taenia, which has served to determine the phylogeny and taxonomy of its species and to understand the level of genetic diversity in the genus. Another important contribution of molecular biology is the identification and production of antigenic molecules used as vaccines candidates or as candidates for serological tests.

Direct use of molecular techniques for NCC diagnosis was first reported in 2006 and demonstrated T. solium DNA in the CSF of 29 of 30 consecutive patients, using a PCR with primers against pTsol9, specific for T. solium.175 Another study, using primers against HDP2, based on a non-coding sequence of T. saginata, which cross-reacts with T. solium, also found parasite DNA in human CSF, as well as reported higher sensitivity by type of NCC (10/14 extraparenchymal NCC cases compared to 4/24 of intraparenchymal, degenerating NCC).

A recent study compared antigen and antibody capture techniques with a pTsol9 PCR. In 150 CSFs of patients with different types of NCC, PCR had the best sensitivity, although its specificity was only 80% using negative controls from Mexico. Unexpectedly, 28/31 patients with only calcified NCC were PCR-positive (compared to 19 antibody-positive and seven antigen-positive by EITB and ELISA-HP10, respectively).Only one study using PCR in porcine cysticercosis has been published, with poor performance: sensitivities of 23% and 32% in heavily infected animals, which improved to 64% using a nested PCR. On the other hand, these PCR assays were 100% specific.

A variety of laboratory methods are available to support the diagnosis of NCC. The LLGP-EITB remains the optimal assay for clinical diagnosis, while antigen detection is useful to monitor patients after anthelminthic treatment. Despite initial reports, molecular methods have not yet proven useful to diagnose NCC in clinical settings. More research is necessary to evaluate their real potential. [18]

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## Neural echinococcosis

Brain involvement with hydatid disease occurs in 1-2% of all Echinococcus granulosus infections. Cerebral hydatid cysts are usually supratentorial, whereas infratentorial lesions are quite rare. Objective of the study was to determine the clinical presentation and surgical outcome of cranial hydatidosis. [19]

Cerebral hydatid disease (neurohydatidosis) is caused by Echinococcus granulosus or less commonly E. alveolaris or E. multilocularis. The larval stage is the cause of hydatid disease in humans.

**Epidemiology:**

Hydatid disease is endemic in the Mediterranean region, the Middle East, Africa, eastern part of Turkey, Australia and parts of South America.

**Clinical presentation:**

Symptoms and signs include:

•focal neurological deficits

•headaches

•increased intracranial pressure

•hydrocephalus

•papilloedema and loss of vision

•altered mental status

•seizures (rare).

**Pathology:**

The infection is acquired via contaminated food with eggs of the tapeworm. The oncospheres released from the eggs in the bowel enters the portal circulation. Hence the liver is most commonly affected, followed by the lung. Other organs may be infected as bones, genitourinary system, bowel and even subcutaneous tissues.

Intracranial hydatid disease is very rare. Most of cerebral hydatid cysts are located in supratentorial structures in the vascular territory of middle cerebral artery.

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**Types:**

Intracranial hydatid cysts can be classified into:

**Primary hydatid cysts:**

◦ occur as direct invasion of larva that managed and filtered via liver and lung to the brain

◦usually solitary but may be multiple

◦is fertile

**Secondary hydatid cysts:**

◦ occur as a result of rupture of primary cysts in others organs then reaching by embolization to the brain

◦usually multiple

◦infertile

◦do not have brood capsule or scolices.

**Radiographic features:**

**MRI**

Described features include:

•well-defined circumscribed spherical non-enhancing intra-axial cystic lesion

•lies in the territory of the middle cerebral artery

•cyst fluid is isointense with CSF in all pulse sequences

•no calcification or and typically no surrounding oedema

◦presence of perilesional edema usually indicates complication as rupture or secondary infection.

**Treatment and prognosis**

Management is surgical, with removal of the entire cyst without rupture using Dowling's maneuver (instilling warm saline between the cyst wall and the brain) 5. In some cases where it is felt that removing the cyst intact (without cyst rupture during surgery) is unlikely to succeed, the cyst can be removed after puncture and aspiration of its contents.

Serology and histopathology of the excised cyst will confirm the diagnosis of neurohydatidosis.

Rupture of the cyst can result in recurrence in the subarachnoid space, both intracranially and of the spine.

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## Paragonimiasis

**Epidemiology:**

Paragonimus spp. is the only mammalian lung fluke capable of infecting humans. An estimated 20 million people are infected worldwide, 10 million in China alone. The "Oriental Lung Fluke," P. westermani, is endemic throughout Asia and Western Africa and is the subspecies most often responsible for human infection. Prevalence of infection is slightly higher in females than males, with a peak in young adulthood. Human Paragonimus spp. infection is most often caused by consumption of freshwater crab or crayfish. Fully cooked crabs and crayfish do not transmit infection, but many regional dishes use pickling or marinating rather than cooking and are potentially infectious. Domesticated cats, dogs, wild boars, and pigs can also harbor the fluke and transmit disease to humans.

**Pathophysiology**:

Once the organism has been ingested, fluke metacercariae are released into the small bowel. Over 2 to 8 weeks, the larvae migrate through the intestinal wall and peritoneum to invade lung parenchyma. The larvae remain in the lungs until maturity, at which time migration recurs. Adult worms may live up to 20 years. Migration to the brain is complicated and the mechanism not well understood; some studies suggest larvae migrate through loose connective tissue around the jugular vein and enter the posterior circulation via the skull base foramina. The predilection of infection for the occipital and temporal lobes supports this theory.

**Clinical findings:**

Initial infection produces gastrointestinal symptoms that can be very mild. Most people recover from the initial infection but death infrequently occurs. During any phase of the disease, migratory subcutaneous masses are often present. Migratory swellings contain immature worms and are most often located over the lower abdominal region but can occur over any skin surface. Within 4 to 6 months of initial infection, pulmonary symptoms develop, ranging from mild cough to fulminant dyspnea or hemoptysis. Active pulmonary disease, either acute or chronic, in combination with neurological symptoms, especially in the absence of tuberculosis, should prompt consideration of paragonimiasis. CNS complications occur in ~1% of patients with pulmonary paragonimiasis. Meningoencephalitis is the most common CNS complication and may persist for 6 to 8 weeks. Symptoms during chronic CNS infection are often vague and may include headache, weakness, or nausea. Other CNS complications include transverse myelitis and myelopathy. Seizures are usually present in patients with more extensive CNS involvement. Untreated CNS disease carries a mortality rate of almost 5%.

**Diagnosis:**

Serum eosinophilia and CSF eosinophilia are often pronounced, regardless of the severity of neurological symptoms. Definitive diagnosis of CNS involvement requires demonstration of

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eggs in CSF or brain biopsy material. Although eggs are often present in the stool, sputum, and peritoneal fluid, serum antibody detection tests are more likely to yield the diagnosis.

Diagnosis is confirmed by detection of antibodies to Paragonimus spp. in the CSF by complement fixation testing.14 because neurological symptoms occur during the chronic phase of disease, CSF examination may not be as helpful as neuroimaging or other diagnostic testing.

**Neuroimaging**:

Plain skull films are often dramatic, demonstrating a characteristic “soap bubble” appearance. As noted earlier, Paragonimus spp. infection has a predilection for the temporal and occipital lobe, and contrast CT usually demonstrates clusters of ring-enhancing lesions in these areas. Brain MRI may reveal additional lesions.

**Treatment:**

Praziquantel is the treatment of choice. Bithional and triclabendazole are also effective but may require repeat or prolonged therapy. Steroids are synergistic with praziquantel but not recommended for use with the other medications.

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## Schistosomiasis (Bilharzia)

### Epidemiology:

Schistosomiasis occurs in up to 300 million people worldwide each year and is caused by five species of blood flukes (digenetic trematodes): Schistosoma mansoni, S. haematobium, S. japonicum, S. intercalculatum, and S. mekongi. CNS involvement has been reported with three of the five species: S. mansoni, S. haematobium, S. japonicum. Humans are definitive hosts, but at least 30 other mammals are also susceptible to infection. Transmission of schistosomiasis requires contact with water, prompting some experts to call it a "man-made disease." Endemicity requires an intermediate mollusk host (aquatic or amphibious snails), but additional factors are also important. In general, countries with poor sanitary facilities and scarce potable water have higher rates of endemicity. Unfortunately, improvements intended to ameliorate poor sanitary conditions and water supplies in developing countries often increase endemicity by damming up or irrigation with polluted infected water. In addition, tourists who are instructed to avoid tap water in endemic countries often miss more subtle forms of contact with the schistosome, such as bathing, washing clothes, and walking barefoot.

### Pathophysiology:

Initial infection occurs when the forked tail of the larvae penetrates human skin. The tail is then shed and the larva migrates into the venous system, favoring venules and venous plexi. Clinical symptoms of schistosomiasis depend upon the infecting species and can occur at several stages during the parasitic life cycle. Each species has a predilection for different sites within the human body: the inferior mesenteric vein (S. mansoni), peri-bladder veins (S. haematobium), or superior mesenteric veins (S. japonicum). Eggs of S. japonicum are smaller than eggs of other schistosomal species and cause 60% of all schistosomal brain infections; the larger egg size of S. mansoni usually limits infection to the spinal cord. S. haematobium may cause either brain or spinal cord infection. Eggs within the CNS do not develop into worms, and adult worms are not believed to migrate into the CNS. Entry into the CNS is theorized to occur via Batson's plexus. Once entry has occurred, eggs induce a granulomatous response as tissues attempt to wall off the invading parasite. During chronic infection, granulomas become exudative and necrotic. Necrosis can be extensive and involve vascular walls as well as local tissue.

### Clinical findings:

Initial infection usually produces an acute febrile infection called Katayama fever with urticarial swellings, myalgias, eosinophilia, and bloody diarrhea. These symptoms may last for several weeks, but are uncommon in populations where infection is endemic. Symptoms may not occur until weeks after the initial infection, especially when caused by S. mansoni or S. japonicum.

Neurological involvement usually appears weeks or months after initial infection when eggs migrate through the vascular system to the brain or spinal cord; symptoms may result from mass effect of the egg itself or from granuloma formation around the egg. Because the parasite likely enters the CNS via Batson's plexus, the spinal cord and posterior fossa are the most common

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sites of involvement. Mass effect produced by granuloma formation can cause increased intracranial pressure, and erosion of vascular walls can produce intracranial hemorrhage. Spinal cord involvement may cause symptoms due to granuloma formation or necrotic myelitis, sometimes resulting in a cauda equina or conus syndrome. Children with schistosomal infection often develop cognitive impairment.

**Diagnosis:**

Definitive diagnosis of CNS schistosomiasis is obtained by identification of an egg in biopsy tissue. Detection of schistosomal eggs in stool or urine confirms the diagnosis of schistosomiasis. Stool examination is more sensitive for S. mansoni and S. japonicum, and examination of urine is best for S. hematobium. Infection can also be confirmed by antibody detection, but antibodies often persist after anthelminthic treatment and should therefore not be used as an indication of the response to treatment. Examination of three stool specimens is more sensitive than immunodiagnosis. For patients with spinal cord infection, CSF ELISA for immunoglobulin G against egg antigens is recommended. When clinical suspicion is high and stool and urine examinations are negative, tissue biopsy should be considered.

**Neuroimaging:**

Although Schistosoma infect the CNS, granuloma formation around the eggs is usually inflammatory and may be mistaken for neoplasm. CT imaging of the brain typically reveals single or multiple hyperdense lesions surrounded by edema with variable contrast enhancement. MRI of the brain may reveal a characteristic “arborized” appearance, with linear enhancement surrounded by punctate enhancing nodules.

**Treatment:**

Praziquantel is effective against all Schistosoma spp. and is curative for 60 to 90% of patients. Patients who continue to shed eggs in feces should be retreated. When praziquantel is ineffective, oxamniquine may be used. Artemether, unlike praziquantel, kills immature migrating larvae (schistosomula) and is synergistic with praziquantel.84 Steroids are recommended for patients with edematous lesions or rapidly progressive neurological deficits. In the absence of edema, addition of steroids to anthelminthic treatment probably does not improve prognosis of either cerebral or spinal cord infection. When large granulomas are present, surgical extirpation is usually warranted.

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## Acanthamoeba histolytica and Balamuthia mandrillaris/Granulomatous Amoebic Encephalitis

### Epidemiology:

Both Acanthamoeba histolytica and Balamuthia mandrillaris are free-living amoebas that cause granulomatous amoebic encephalitis (GAM). Both are present throughout the world in soil and sometimes in freshwater. Although both organisms are capable of living in water, they are not encountered as frequently as Naegleria spp., and stagnated water is not a requirement.

Acanthamoeba histolytica has been isolated from water fountains and contact lens and is a common cause of self-limited and mild keratitis.

### Pathophysiology:

CNS infection by A. histolytica is uncommon in immunocompetent hosts. In contrast to A. histolytica, B. mandrillaris causes infection in immunocompetent and immunosuppressed hosts with equal frequency.

### Clinical findings:

Until 1997, all human cases of B. mandrillaris infection had been diagnosed at autopsy. Clinical presentation is similar to A. histolytica infection. No systemic findings are specific for either infection. Encephalitis develops more slowly with B. mandrillaris infection and often takes months until clinical symptoms develop. Immunosuppressed hosts are more likely to develop a virulent hematogenous or cutaneous infection or granulomatous meningitis.

### Diagnosis:

Definitive diagnosis can be obtained by demonstration of trophozoites or cysts of A. histolytica on stained smears of biopsy specimens or corneal scrapings. Direct IFA tests can be useful. Differentiation between B. mandrillaris and A. histolytica infection requires immunofluorescence studies. Examination of contact lenses from patients with keratitis can reveal A. histolytica.

### Neuroimaging:

Contrast-enhanced head CT of patients with B. mandrillaris CNS infection usually demonstrates ring-enhancing lesions. MRI shows diffusion-restriction within the abscess cavity and prominent edema on T2 that can resolve after treatment. Calcifications are seen in patients with chronic infection.

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**Treatment:**

There are no standardized treatments for CNS infection with either B. mandrillaris or A. histolytica. In children, successful treatment has included trimethoprim-sulfamethoxazole, rifampin, and ketoconazole. Eye and skin infections are treatable, but if the CNS is infected, death usually occurs within weeks to months. [21]

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## Strongyloidiasis

### Epidemiology:

Strongyloidiasis is a human intestinal infection most often caused by Strongyloides stercoralis. Other subspecies, such as S. fulleborni, although pathogenic in primates, typically cause only minor infections in humans. Historically, strongyloidiasis had been confined to tropical and subtropical regions, but infection is increasingly common in Europe and the United States. In the United States, cases are encountered primarily in tertiary medical centers, especially in the Mid-Atlantic region. In addition, with the advent of HIV infection and more frequent use of immunosuppressant medications, more people in the developed and developing world are at risk for contracting this infection and for developing hyperinfection.

### Pathophysiology:

Strongyloides spp. are capable of living as parasites or free-living organisms. There are three developmental stages: filariform (infective), rhabditiform, and adult. Rhabditoid larvae can become filariform or differentiate into male or female and maintain the rhabditiform cycle indefinitely. Strongyloidiasis is most prevalent in areas of poor sanitation and is usually acquired through contact with the parasite in contaminated water or by direct penetration of the skin by the filariform larvae. In addition, host autoinfection can occur when the parasite completes its life cycle within the host. After entering a human host, the parasite enters the venous circulation, migrates through the lung alveoli, and eventually burrows into the small intestine, where it can reside for up to 50 years. From this site, worms can be released into the stool or develop into the filariform state and reinfect the host. Infection also facilitates coinfection with other agents, sometimes resulting in overwhelming bacteremia with dissemination to the CNS and other organs. Disseminated S. stercoralis infection is more likely to occur in the immunocompromised host. Massive worm burden, known as hyperinfection syndrome, may occur when the usual parasitic life cycle is accelerated. Hyperinfection is usually limited to the gastrointestinal tract or lungs and is rare in the CNS.

### Clinical findings:

Infection may persist for many decades without producing symptoms. Acute disease is limited to the gastrointestinal tract and lungs. Patients often develop wheezing, diarrhea, and postprandial abdominal pain. Transient low-grade fever is common. Chronic disease develops over days to weeks and usually includes a dermatological manifestation called larva currens. The perianal region is the initial site of involvement, but most patients do not notice this early manifestation. The larvae migrate at a rate of up to 5 cm/d and travel subcutaneously or internally to other organs. Disseminated disease can produce infection in other organ systems, including the CNS.

Alteration in mental status and meningismus are the most common manifestations of CNS involvement, but penetration of vessel walls can produce mycotic aneurysm and intracranial hemorrhage, even vasculitis. If bacterial hyperinfection develops, brain abscess, caused by Escherichia coli in ~30% of cases, may produce focal neurological symptoms.

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**Diagnosis:**

Serum eosinophilia is common during primary infection but wanes with dissemination of infection. Diagnosis can be confirmed by identification of Strongyloides spp. rhabditiform larvae in stool, serum, CSF, or peritoneal fluid. Larvae do not appear in the stool until approximately 1 month after initial infection. In patients with disseminated infection, larvae may also appear in the sputum. Larvae can be detected in duodenal secretions with the Entero-test (Hedero, Palo Alto, CA); a weighted gelatin capsule is swallowed, the gelatin dissolves allowing the string to pass into the duodenum and 4 hours later the string is removed and examined for larvae. Due to the low sensitivity of direct identification tests, testing of serial samples is recommended, especially for stool specimens. If strongyloidiasis is suspected but not detected by direct identification tests, antibody detection testing should be performed. Unfortunately, antibody detection tests cannot distinguish between past or present infection, can be negative in patients with disseminated infection, and may cross-react with other helminthic and filarial infections. Of the available antibody tests, enzyme immunoassay has the highest sensitivity (~90%).

**Neuroimaging:**

In patients with chronic infection, neuroimaging is often nonspecific, but atrophy may be prominent. Additional abnormalities include abscess formation or mycotic aneurysms, either of which may occur along any vascular distribution but usually spare the extracranial vascular system.

**Treatment:**

Ivermectin is the treatment of choice, but thiabendazole, albendazole, and mebendazole are also effective. Steroids should not be used during acute infection, as they may promote dissemination. Disseminated disease carries a mortality rate of almost 80%, so early detection and treatment is imperative.

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## Toxocariasis

### Epidemiology:

Toxocariasis is endemic in all parts of the world. Most human Toxocara spp. infections are caused by T. canis, but T. cati, and T. leonina infections also occur. Recent studies suggest that living in a rural area, ownership of dogs, and dementia are associated with a higher risk for CNS T. canis infection. Children who eat earth (geophagia, pica) are also at higher risk of becoming infected. An infected dog or cat can excrete up to one million eggs each day, and eggs can survive in the environment for many years. Some experts have disputed the role of dogs as vectors of transmission, noting that up to half of patients do not own a pet and cannot recall any close animal contact. In northern industrialized countries, seroprevalence of this infection is 5% in urban adults and up to 40% in children and rural farmers. In the West Indies and Bali, seroprevalence rates approach 80%.

### Pathophysiology:

Introduction into a human host is accidental and occurs by ingestion, most often on contaminated hands. Once in the human gastrointestinal tract, eggs remain in the small bowel for a short period, hatch into second-stage larvae, and then migrate to the liver. Larvae then enter the portal circulation and migrate through small-caliber vessels to the viscera, producing a mild inflammatory response along the migratory path.28 Chronic inflammation can eventually induce granuloma formation. Migration to the brain is uncommon but usually produces a more dramatic inflammatory response than migration through the periphery.

### Clinical Findings:

Toxocariasis is almost always a benign self-limited disease, but ocular or cerebral involvement can cause significant morbidity, and infection in the elderly can be fatal. Symptoms depend on the disease burden and system infected, but weakness, lethargy, fever, and headache are common. Visceral larva migrans occurs mainly in children with disseminated infection and can produce granulomas in the liver, lungs, kidneys, heart, muscle, brain, or eye. Ocular involvement, known as ocular larva migrans, can produce symptoms of optic neuritis or blindness and occurs when the parasite migrates to the optic nerve head. Infection can also produce ocular findings similar to retinoblastoma; as retinoblastoma is treated by enucleation, toxocariasis should be excluded as an etiology before such treatment is considered. Although the majority of human Toxocara spp. infections are asymptomatic, subtle cognitive symptoms may not be appreciated or attributed to other behavioral conditions. Unlike other human nematode infections, cognition is affected during almost all chronic Toxocara spp. infections and can range from hyperactive behavior in children to dementia in elderly adults.

### Diagnosis:

Toxocara spp. larvae are only rarely identified in clinical specimens. Because the parasite enters the human host as a mature adult, eggs are not isolated in stool. Detection of eggs from other organisms, such as Ascaris and Trichiuris, suggests exposure to fecal material where Toxocara may also reside. Serum and CSF eosinophilia is a frequent finding, but treatment can reverse this

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abnormality, and chronic infections may have a blunted eosinophilic response. Antibody testing for second-stage T. canis excretory-secretory larval antigens (TESAg) is sensitive and specific for visceral larva migrans provided the serum is pretreated to remove cross-reacting antibodies to organisms such as Ascaris suum. TES-Ag testing can be performed on blood or CSF samples.

**Neuroimaging:**

Contrast-enhanced head CT often demonstrates vasogenic edema and a heterogeneous enhancement pattern resembling malignant gliomas. MRI imaging can reveal subcortical and white matter disease, resembling small vessel vasculitis. Imaging abnormalities suggestive of small infarctions on FLAIR and T2 sequences often demonstrate microhemorrhages on gradient-echo sequences.

**Treatment:**

Although diethylcarbamazine is the treatment of choice, mebendazole and albendazole are also effective against toxocariasis. Suggested length of treatment is 3 to 4 weeks. In patients with ocular involvement, steroids should be administered and an ophthalmologist consulted. [(22)]

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**References:**


1-https://en.wikipedia.org/wiki/Behavior-altering_parasite

2-https://academic.oup.com/beheco/article/10/3/234/201488

3-https://www.ncbi.nlm.nih.gov/pubmed/19067631

4-https://www.cdc.gov/parasites/toxoplasmosis/gen_info/faqs.html

5-http://apps.who.int/medicinedocs/en/d/Js2215e/4.1.html

6-https://www.mayoclinic.org/diseases-conditions/toxoplasmosis/symptoms-causes/syc-20356249

7-https://radiopaedia.org/articles/neurotoxoplasmosis

8-https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2526127/

9-http://www.who.int/mediacentre/factsheets/fs259/en/

10-https://www.ncbi.nlm.nih.gov/pmc/articles/PMC338269/

11-http://jnnp.bmj.com/content/69/4/433

12-https://www.cdc.gov/parasites/naegleria/index.html

13-https://www.cdc.gov/parasites/naegleria/pathogen.html

14-https://www.cdc.gov/parasites/naegleria/illness.html

15-https://www.cdc.gov/parasites/naegleria/diagnosis.html

16-https://emedicine.medscape.com/refarticle/215589-clinical?src=refgatesrc1

17-https://emedicine.medscape.com/article/1168656-clinical

18-https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4005112/

19-https://www.ncbi.nlm.nih.gov/pubmed/20929036

20-https://radiopaedia.org/articles/cerebral-hydatid-disease-1

21-https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2683840/

22-https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2678030/

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