Part II – Neurological Disorders

CHAPTER 7
PROTOZOAL AND HELMINTHIC INFECTIONS

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NEUROLOGY IN AFRICA

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CHAPTER 7

PROTOZOAL AND HELMINTHIC INFECTIONS

This chapter is concerned with the main protozoal and helminthic infections affecting the nervous system in Africa. These include cerebral malaria, toxoplasmosis, and human African trypanosomiasis (HAT), neurocysticercosis, schistosomiasis and hydatid disease. The student should aim to be familiar with these, including life cycles, clinical presentations, diagnosis, management and prevention.

CEREBRAL MALARIA

Cerebral malaria is a severe neurological disease of the brain that is caused by *Plasmodium falciparum* and is characterized by fever, altered level of consciousness and laboratory evidence of malaria infection. The research definition of cerebral malaria is unrousable coma, (Glasgow coma scale ≤8 or Blantyre coma scale for young children ≤2 (Table 7.2) in the presence of a peripheral parasitaemia after other causes of coma have been excluded.

Epidemiology

Each year there are over 300 million new cases of malaria in Africa resulting in over 1 million deaths there, occurring mostly but not exclusively in children. Cerebral malaria is one of the most important complications. It is invariably fatal without treatment and each year there are over half a million new cases of cerebral malaria in Africa. Most cases occur in non immune children (<5 yrs) and the incidence declines progressively as children become older. Cerebral malaria also occurs in adults but much less frequently. The mortality rate in treated cerebral malaria in children is 15-20% and 10-15% in adults. Recent reports and clinical experience in Africa suggest that the overall burden of severe malaria is decreasing significantly there.

Pathophysiology of cerebral malaria

The mechanism of brain injury in cerebral malaria is not fully understood. The main theories involve parasite sequestration, endothelial dysfunction and injury with cytokine release and blood brain barrier dysfunction. The brain at post mortem in cerebral malaria is typically congested and darkened in colour (Fig 7.1). The histopathology shows many parasitized red blood cells (RBCs) sequestered in the capillaries and small blood vessels particularly in the grey matter and petechial perivascular ring haemorrhages in white matter (Fig 7.1). The sequestration is attributed to cytoadherence or the sticking of parasitized RBCs to vascular endothelium and to rosetting; the sticking of unparasitized RBCs around a parasitized RBC, which in turn may lead to congestion of the capillaries. These findings have led to the mechanical theory of decreased microcirculation or blocked capillaries being a main mechanism. An alternative

theory is that sequestration and rupture of trapped parasitized RBCs release many mature malaria parasites, trophozoites and schizonts leading to increased local glucose consumption and massive local release of endotoxins and cytokines. These in turn result in breakdown in the blood brain barrier, increased cerebral blood flow, cerebral oedema and coma.

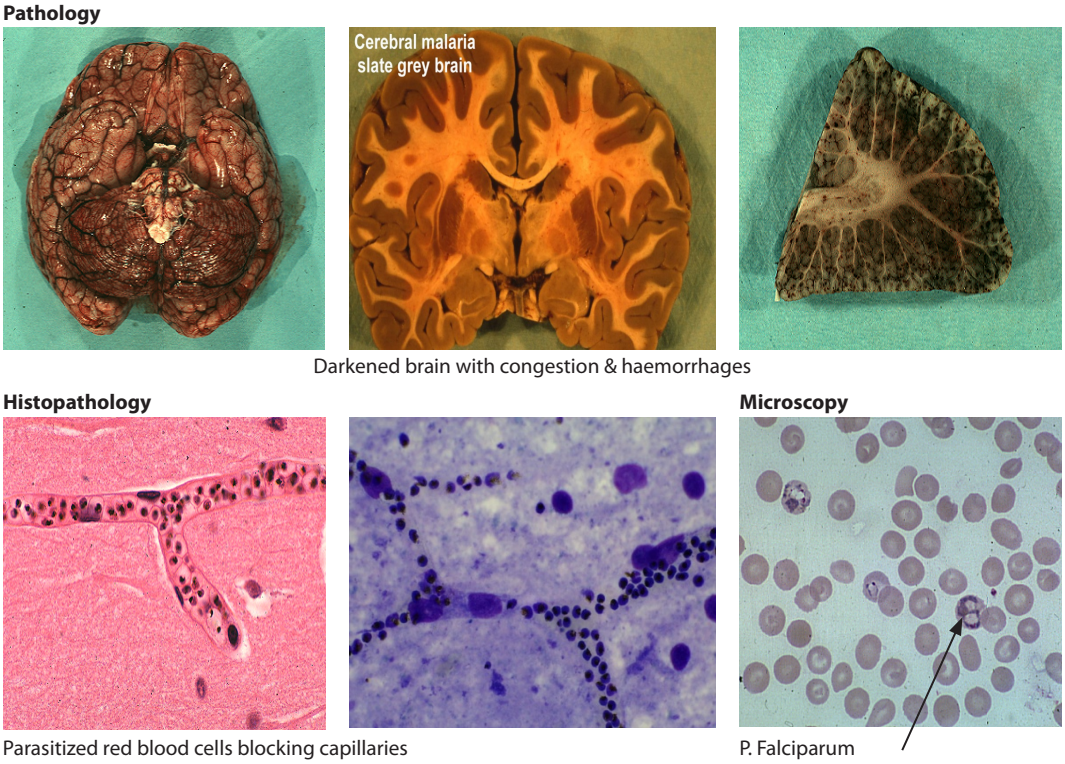


Figure 7.1 Brain in Cerebral Malaria (CM)

Clinical features

The first symptoms of cerebral malaria in adults include fever, headache, myalgia, malaise followed by progressive drowsiness, confusion, delirium, stupor and coma. These symptoms usually develop over 1-3 days but may occur in <24 hours. The onset can be relatively sudden with the patient presenting with a febrile illness over hours followed by a generalised seizure and or coma. This is a more common presentation in children and in non immune hosts. Seizures occur in >50% of children and about 20% of adults, either at onset or throughout the course of the illness. In adults the main neurological findings are those of an acute encephalopathy with symmetrical upper motor neurone signs. These include altered level of consciousness, divergent gaze, bruxism (teeth grinding), hypertonia and extensor plantar reflexes. The duration of coma after starting treatment is on average 1-3 days but may persist for longer in adults. Systemic complications include anaemia, acidosis, renal failure, respiratory distress syndrome and secondary bacterial sepsis.

A characteristic malaria retinopathy has recently been described in Malawi occurring in children and also in adults with cerebral malaria (Fig. 7.2). This retinopathy is characterized by areas of

retinal whitening best seen immediately around the macula/fovea but sparing it, coupled with white or orange discolouration of some retinal vessels and capillaries. These features are now considered to be specific for cerebral malaria. They are best seen with the direct ophthalmoscope provided that the pupils have been dilated and the examiner is already familiar with them. The more classical fundoscopy findings in cerebral malaria include retinal haemorrhages (<10% of adults) and papilloedema (<1% of adults). Characteristic white centered retinal haemorrhages are found in most children and papilloedema in 10%. These however are not specific for cerebral malaria.

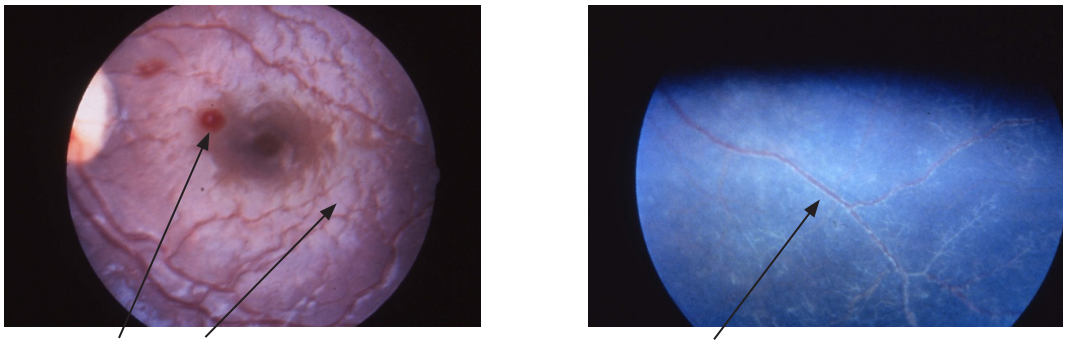


Figure 7.2 Retina in CM. *Photographs courtesy of Susan Lewallen Ophthalmology Dept, KCMC*

Differential diagnosis

The high prevalence of asymptomatic parasitaemia may make the diagnosis less certain and therefore other causes of encephalopathy need to be excluded. Infectious causes include acute bacterial meningitis (ABM), partially treated ABM, viral meningoencephalitis including rabies, semi acute presentations of the main HIV related CNS infections including cryptococcal and tuberculous meningitis and toxoplasmosis. Non-infectious causes include metabolic abnormalities, intoxication, epilepsy, stroke and other causes.

Diagnosis of malaria

The diagnosis of cerebral malaria is supported by laboratory evidence of infection. This is usually done by the demonstration of malaria parasites on a peripheral blood slide. A blood slide, usually a thick film is taken first on admission, after the first 24 hours and again at 48 hours. A negative blood slide on admission needs to be repeated if cerebral malaria is still suspected.

Newer methods of diagnosis include rapid diagnostic tests (RDT) which detect parasitic enzymes or antigen in whole blood. Most are sensitive and specific for *P. falciparum* and are very helpful particularly where skilled microscopy is unavailable. RDTs based on antibody detection are of less value clinically as they don't distinguish between old or recent infection and are non specific for falciparum.

A full blood count is frequently normal but may show anaemia especially in children. The presence of leucocytosis and thrombocytopenia usually indicates severe systemic malaria or coexistent sepsis. Hypoglycaemia is common in severe malaria particularly in children and blood glucose should always be regularly checked in cerebral malaria. Other investigations

include renal, liver function, coagulation screen, arterial and blood gases. Urine in malaria may rarely be dark or black in colour and an analysis shows red blood cell casts. CSF examination is clear in colour with no increase in cells but may show a slightly elevated opening pressure with a mild elevation in protein. Neuroimaging is typically normal.

Key points

- cerebral malaria is a major cause of death in children <5 yrs
- clinical features include headache, fever, myalgia, altered consciousness & seizures
- symptoms typically progress over 1-3 days
- diagnosis is supported by evidence of malaria parasites in blood
- other causes of encephalopathies need to be excluded

Treatment of cerebral malaria

The treatment of a patient with cerebral malaria is based on specific drug treatment and the early recognition and management of complications. Management of complications includes urgent measures to treat hypoxia, hypoglycaemia, seizures, hypovolaemia, anaemia and acidosis. Because most deaths in cerebral malaria occur within 24 hours of onset, patients should if possible be admitted to a high dependency care area or an intensive care unit and have emergency management. Blood sugar should be checked every 4-6 hours particularly in children because of recurrent hypoglycaemia. Fluids need to be restricted in the first 48 hours, if raised intracranial pressure is suspected. Complicated cases may need intubation, ventilation, exchange transfusion and dialysis if available. A summary of the steps in emergency management of complications is outlined below.

Management of complications of cerebral malaria

- maintain airway with oxygen if hypoxaemic or in respiratory distress
- if high fever present reduce temperature with paracetamol
- correct hypovolaemia in children with NS, infusion @ 2-3 ml/kg/hr ↓
- treat hypoglycaemia with iv bolus one ml/kg of 50% dextrose
- give 5-10% dextrose infusion to all cerebral malaria patients to prevent hypoglycaemia
- control seizures using either diazepam or lorazepam or phenytoin/phenobarbitone
- offer blood transfusion if the haematocrit is <15% in children or <20% in adults
- give fresh whole blood, frozen plasma and vitamin K for spontaneous bleeding
- give first-line antibiotics for possible pyogenic meningitis and sepsis until excluded
- ventilate adults with respiratory distress syndrome and refer for dialysis if in renal failure

Specific drug treatment

The specific drug treatment of cerebral malaria includes the artemisinin compounds and quinine (Table 7.1). Recent studies in severe malaria show that parenteral artemisinin compounds are superior to quinine; they are easier to administer, better tolerated with no major side effects and have a better outcome. Intravenous artesunate was shown to be more potent than quinine (35% greater reduction in mortality rate) in treating cerebral malaria in adults in Vietnam. It is also more potent than artemether, possibly because of a more rapid effect. Parenteral artesunate is now the drug of first choice in the treatment of cerebral malaria in Africa.

Meanwhile quinine is still being used for the treatment of cerebral malaria in many countries in Africa and its use should never be delayed if artemisinins are unavailable. The main side effects of quinine are cinchonism (tinnitus, deafness, dizziness, nausea and vomiting), cardiac depression, hypotension, hypoglycaemia, blindness and very rarely blackwater fever. Quinine should also be used cautiously in patients with heart disease and in the elderly. In adults a loading dose of 20 mg/kg is given iv over 2-4 hours and then continued by iv infusion at 10 mg/kg/8 hourly for 5 days or until able to take orally. After 3 days of iv treatment the dose can be reduced from 8 to 12 hourly. Intramuscular quinine administered according to instructions can be used if iv route is not possible.

Table 7.1 Drug treatment of cerebral malaria

Drug	route	Dose loading	Dose maintenance	Duration
artesunate	iv	2.4 mg/kg	2.4 mg/kg/ @ 12 and 24 hours & then daily	7 days
or				
artemether	im	3.2 mg/kg	1.6 mg/kg/daily	5 days
or				
quinine dihydrochloride	iv	20 mg/kg (max 1400 mg) over 4 hours in 5% dextrose or dextrose/saline	10 mg/kg/8 hourly*	5 days

** infused over four hours in adults & changed to oral as soon as the patient can swallow*

Prognosis in Cerebral Malaria (CM)

The mortality rate in quinine and artemisinin treated children with cerebral malaria in Africa is 15-20%. Mortality rates are lower <10%, in both artemisinin and quinine treated adult patients. However mortality rates in pregnancy are up to 50%. Risk factors for death in cerebral malaria in adults include anaemia, seizures, respiratory distress syndrome and renal failure. Prolonged and deep coma, elevated intracranial pressure and hypoglycaemia are risk factors in children. While the majority of patients make a full recovery from treated cerebral malaria, permanent neurological deficits still occur in >20% of children and <5% adults. Deficits including psychoses, ataxias are usually transient and clear within weeks or months. Gross neurological deficits occur in about 10% of children, these include, hemiparesis, quadriparesis, cerebellar ataxia, and severe brain damage. Neurocognitive and behavioural dysfunction are also more common occurring in >20% and epilepsy occurs in about 10%. Hemiparesis is the main deficit in adults.

Key points

- parenteral artemisinin is superior to quinine in treatment of cerebral malaria
- mortality in treated children is 15-20% and <10% in adults
- morbidity occurs in >20% of children and <5% adults
- morbidity (children), neurological & cognitive deficits, behavioural abnormalities & epilepsy
- hemiparesis is most frequent complication in adults

Table 7.2 Blantyre coma scale*

To obtain coma score add the scores from each section**	
Best motor response	
Localizes painful stimulus	2
Withdraws limb from painful stimulus	1
No or inappropriate response	0
Best verbal response	
Cries or speaks appropriately with painful or verbal stimuli	2
Moans or abnormal cry to painful stimulus	1
No vocal response to painful stimulus	0
Eye Movements	
Watches or follows e.g. mother's face	1
Fails to watch or follow	0

** for use in children*
*** Score ≤2 & a positive blood slide suggests cerebral malaria*

TOXOPLASMOSIS

Introduction

Toxoplasmosis is caused by infection with *Toxoplasma gondii*. T. gondii is an intracellular protozoan parasite whose definitive host is the cat. Humans and other animals may become infected accidentally from infected cats via ingestion of food or water contaminated with cat faeces. Transmission in Africa is most probably from ingestion of undercooked meat of infected animals. Human infection occurs mostly during childhood and antibody seroprevalence rates are a measure of latent infection. Worldwide seroprevalence rates vary from 20% to 75% and a similar pattern occurs in Africa varying from 27% in Uganda to 75% in Nigeria. Nearly all toxoplasmosis illnesses in Africa are caused by reactivation of latent infection in HIV related immunosuppression. Cerebral toxoplasmosis or toxoplasma encephalitis (TE) is the main form of the disease resulting from reactivation. The frequency of cerebral toxoplasmosis in HIV varies within Africa, depending on the local pattern of latent infection. In one major HIV autopsy study in West Africa, evidence of cerebral toxoplasmosis was present in15% and was considered the main cause of death in 10%. Toxoplasmosis is considered to be the most common cause of a focal brain lesion in AIDS patients in most parts of Africa.

Clinical presentation

Clinically patients present sub acutely over days or more commonly 1 or 2 weeks with headache and fever often in combination with focal neurological signs. Focal neurological signs occur in around three quarters of patients and include hemiparesis, cranial nerve palsies, ataxia, confusion, altered consciousness and seizures. The pattern of neurologic signs will depend on the site of the focal lesion within the brain and its duration. There may be associated toxoplasma chorioretinitis in 5-10% of affected patients. Cerebral toxoplasmosis occurs mainly in patients with a CD4 count of <100 cells/mm^3 and is frequently the first presenting complaint of HIV infection.

Diagnosis

Laboratory investigations are of limited value in the diagnosis. A positive serological screening test for toxoplasmosis usually indicates previous exposure rather than active disease. However a negative result does not exclude the disease. The CSF is also non diagnostic showing

predominantly lymphocytes with an elevated protein and a modest decrease in glucose. CT scan of the head with contrast is very helpful for the diagnosis. In cerebral toxoplasmosis, it shows a single or more commonly multiple ring-enhancing lesions with surrounding oedema situated usually in the basal ganglia or/and at the junction of the grey white matter in the cortex (Fig 7.3).

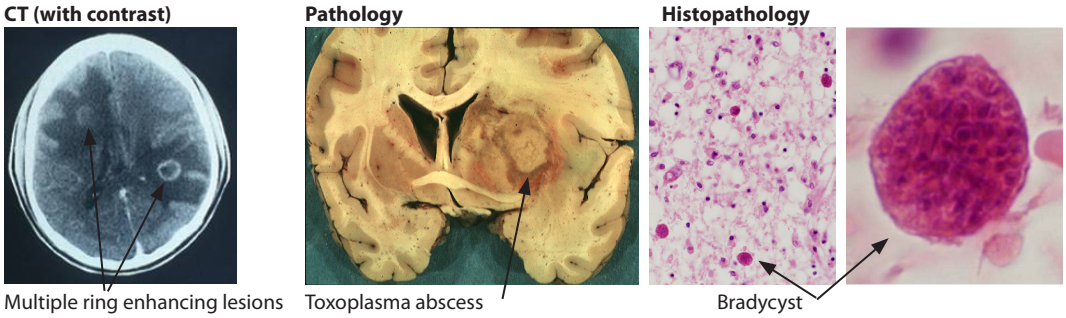


Figure 7.3 Brain in toxoplasmosis

Differential diagnosis

The differential diagnosis of cerebral toxoplasmosis includes other causes of focal neurological disorders in HIV disease, including tuberculoma, primary CNS lymphoma, and rarely progressive multifocal leucoencephalopathy (PML). Other HIV related infections including cryptococcal and TB meningitis may also need to be considered. The clinical presentation of tuberculoma can be very similar to that of cerebral toxoplasmosis, although the clinical course in tuberculoma is usually slower and there may be evidence of concomitant TB elsewhere e.g. chest X-ray. CT features of tuberculoma in adults are those of a single or multiple ring enhancing lesions, with irregular walls of varying thickness and surrounding oedema situated mainly in the cortex. Primary CNS lymphoma is relatively uncommon in HIV in Africa occurring in <1% of HIV patients. The CT in lymphoma may be similar to toxoplasmosis and shows ring enhancing lesions in the deep white matter near the corpus callosum or subependymal areas. In the absence of a CT scan empirical treatment for toxoplasmosis should be started in all HIV patients presenting with focal neurological signs and CD4 count <200 cells/mm^3.

Key points

- toxoplasmosis is the most common cause of focal brain lesion in AIDS
- occurs mostly in patients with CD4<100 mm^3
- clinical features include headache, fever & focal neurological signs over days or weeks
- diagnosis supported by ring enhancing lesions on CT brain scan
- differential diagnosis includes tuberculoma & lymphoma

Treatment

Treatment is based on drugs that interfere with the ability of *T. gondii* to synthesise folate and replicate. High dose trimethoprim/sulphamethoxazole (TMP-SMX) is the recommended first line treatment for cerebral toxoplasmosis in Africa (Table 7.3). The dose is one TMP-SMX tablet (80/400 mg) for each 8 kg body weight, taken in two or three divided doses per day. For the average adult this is usually 4 tablets, (1920 mg) twice daily for four weeks, followed by

two tablets twice daily for another 8 weeks. Long term secondary prophylaxis with two tablets daily is indicated if the CD4 count is <200/cm^3 and should be considered for all patients with CD4 counts < 350 cells/cm^3. A clinical response to treatment is usually seen within 3-4 days of starting treatment and definite improvement after 2-3 weeks in over 80% of patients. If there is inadequate or no response to treatment, then other diagnoses other than toxoplasmosis should be considered including tuberculoma. Relapses should be retreated with full course (TMP-SMX). Patients who are intolerant of TMP-SMX because of drug rash or neutropenia can be treated with pyrimethamine 50-75 mg daily in combination with clindamycin 600 mg 8 hourly or azithromycin 1 gram daily. These are continued for a total of 6 weeks. Limiting side effects include drug rashes and bone marrow depression. Folinic acid 15 mg daily should be prescribed with pyrimethamine.

Prognosis

The mortality in Africa in treated cases of cerebral toxoplasmosis is 10-15% mainly because of late disease and co-morbidity in HIV disease. Relapse rates are considered to be in the order of 20%, occurring up to 6 months after successful treatment. Antiretroviral therapy (ART) should be started within two weeks of starting treatment for suspected or proven toxoplasmosis.

Key points

- treatment is with high dose TMP-SMX for 4/52 & maintenance dose for 8/52
- long term chemoprophylaxis should continue until CD4 is >350 cm3
- ART should start within two weeks of starting treatment
- case fatality rate in treated cases is 10-15%

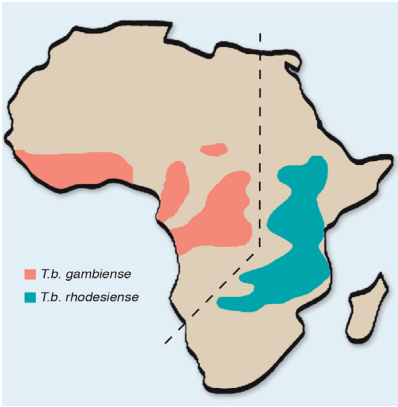
Table 7.3 Drug treatment for toxoplasmosis

Drug	Dose/route	Duration	Side effects
trimethoprim/sulphamethoxazole (TMP-SMX)			
treatment phase	4 tab (1920 mg) /po/ twice daily	4 weeks	rash, neutropenia
maintenance phase	2 tab/po/twice daily	8 weeks	
chemoprophylaxis phase	2 tab/po/ daily	until CD4 >350/cm3	

HUMAN AFRICAN TRYPANOSOMIASIS (HAT)

This is a protozoan parasitic infection caused by parasites of the ***Trypanosoma brucei,*** which are transmitted to humans by the bite of the tsetse fly (*Glossina* spp) (Fig 7.4). Human African trypanosomiasis (HAT), better known as sleeping sickness, is restricted to the distribution of tsetse flies in a vast area throughout sub-Saharan Africa (Fig 7.4). It stretches from 14° north to 20° south latitude, putting a total of over 60 million people in 36 countries at risk. HAT occurs in both epidemic and endemic forms. There are two main types of HAT with differences in epidemiology, biology and clinical features: ***Trypanosoma brucei rhodesiense*** **(T.b.r.)** affects eastern and parts of southern Africa with savannah bush with game animals and cattle as its main reservoir. It accounts for fewer than **5%** of reported cases and causes an

acute illness. ***Trypanosoma brucei gambiense*** **(T.b.g.)** affects Central and West African river and water hole areas with humans as its main reservoir; it accounts for over **95%** of all cases and causes a chronic illness. In Uganda both types of HAT occur, indicating local geographical overlap between **Tbr** and **Tbg** infections. The people most at risk live in rural areas and depend on agriculture, fishing, animal husbandry and hunting in African rivers and waterhole areas. HAT has re-emerged during the last decades as a threat to public health in those affected areas. Precise details of disease prevalence are difficult to ascertain. It is estimated that around 300,000 people in Africa are infected with most of those occurring in Southern Sudan and the Democratic Republic of Congo (DRC). Of those approximately 40,000 cases are reported annually to WHO.



Main sleeping sickness areas in Africa

Tsetse fly

Figure 7.4 Map of trypanosomiasis distribution in Africa

Key points

- thousands cases of HAT or sleeping sickness occur annually in Africa
- HAT is transmitted by tsetse fly bites & people most at risk live in rural areas
- two main types, T. b. r in E. & S. Africa and T. b. g in C. & W. Africa
- wild animals and cattle are the main reservoirs of infection in E. & S. Africa
- infected humans are the main reservoir in C. & W. Africa

Clinical features

Tsetse flies acquire the infection by feeding on infected humans **(Tbg)**, wild animals or domestic cattle **(Tbr)**. The disease can also be transmitted vertically from mother-to-child and occasional accidental infections have occurred in the laboratory, mostly from needle stick injuries. The tsetse fly becomes infective approximately 3-5 weeks after biting an infected animal or human and later may transmit the trypanosomes to humans by biting. HAT may begin in humans at the site of the bite, as a painful indurated erythematous boil-like lesion or **primary chancre**. The primary chancre starts 3-15 days after the bite increasing to a couple of centimetres in size over the following 2-3 weeks. It usually does not suppurate and then slowly clears leaving a mark on the skin. Primary chancre formation occurs in less than half of cases of T.b.r. cases and is uncommon in T.b.g. The trypanosomes multiply at the chancre site, then invade the blood

stream and lymph nodes and may eventually cross the blood–brain barrier and infect the brain. This invasion gives rise to two characteristic clinical stages, the early or **haemolymphatic stage** and the late, or **encephalitic stage**. T.b.g infection is characterised by distinct stages, a long asymptomatic phase followed by a sub acute illness and a chronic, late encephalitic stage, with the whole illness lasting up to 3 years or more before death in untreated cases. T.b.r infection presents with a more acute illness and less distinct stages with 80% of deaths occurring within 6 months of onset in untreated cases. The life cycle is outlined below in Figure 7.5.

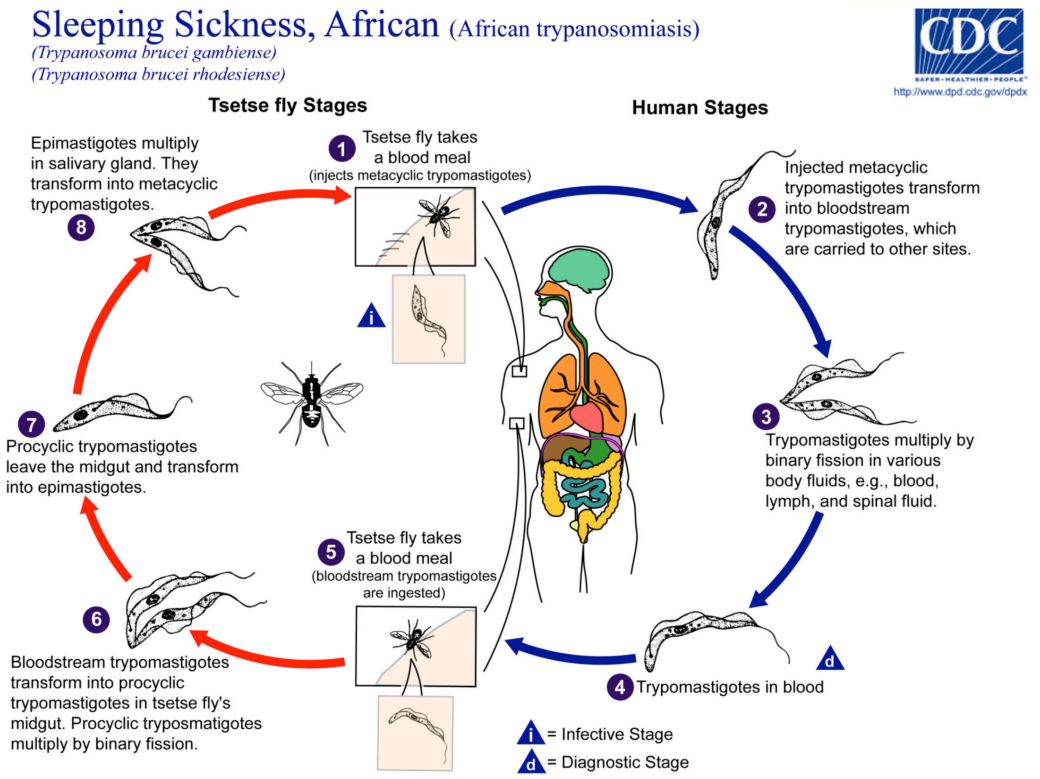
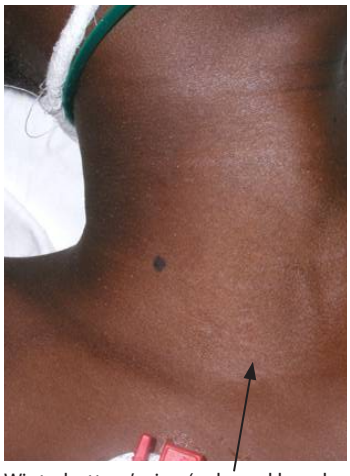


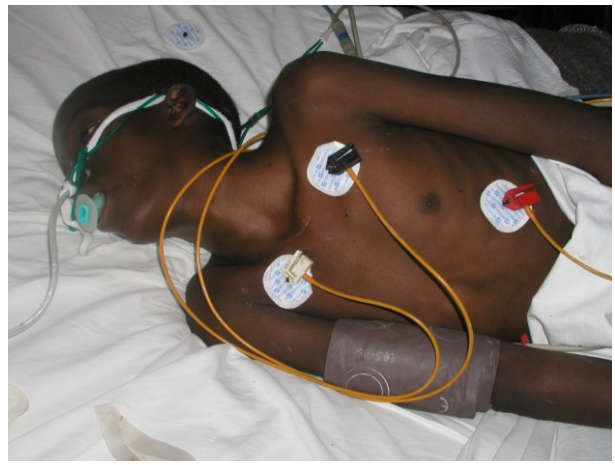
Figure 7.5 Life cycle for trypanosomiasis

Haemolymphatic stage

The onset is variable but usually occurs 1-3 weeks after the bite. Irregular episodes of fever lasting 1-7 days occur together with generalised lymphadenopathy. Palpable lymph nodes in the cervical triangle of the neck are called **Winterbottom's sign** (Fig. 7.6). Early associated symptoms include headache, joint pains, weakness and weight loss. Systemic involvement may then occur with multiple organs affected. In **T.b.r** this is characterised by fevers, pleural and pericardial effusions, myocarditis, hepatosplenomegaly, jaundice, anaemia and endocrine disorders. This stage in **T.b.r** can be fatal within weeks or more commonly progresses to the late encephalitic stage. In **T.b.g,** this early stage is usually less pronounced and more chronic and is characterised by hepatosplenomegaly and skin involvement. It may last many months to a couple of years before progressing on to the late or encephalitis stage.



Winterbottom's sign (enlarged lymph glands)



Encephalitic stage (late)

Figure 7.6 Clinical findings in trypanosomiasis

Encephalitic stage

After the haemolymphatic stage, HAT may remain quiet until invasion of the CNS takes place. There is not always a clear recognisable transition from early to late stage disease. In **T.b.r**. disease this occurs within weeks or months of onset, whereas in **T.b.g** disease the late stage takes months or years to develop. The onset of encephalitis is often subtle and unnoticed and neurological presentations are variable. These can be generally grouped into behavioural and psychiatric symptoms, motor, sensory disorders and sleep disorders all of which may overlap. Behavioural and psychiatric presentations vary from irritability, headache, personality and habit change, to agitation, psychosis and mania with confusion and sleep. Accompanying motor signs include limb tremors, incoordination, dysarthria, involuntary movements, pyramidal and extra pyramidal findings. Sensory complaints include pruritus, painful hyperaesthesia and polyneuritis. The sleep disturbances include undue tiredness and an uncontrollable urge to sleep during the day time accompanied sometimes by insomnia at night. Untreated the disease eventually progresses to immobility, seizures, continuous sleep, coma and eventually death (Fig. 7.6). Late stage neurological features may not be seen in **T.b.r** as coma and death may intervene.

Diagnosis

HAT is diagnosed in Africa on the basis of characteristic clinical findings in a patient coming from an endemic area and confirmed by laboratory investigations. Other causes of febrile diseases especially malaria, HIV and TB need to be considered. Routine laboratory investigations may show a mild anaemia and elevated erythrocyte sedimentation rate (ESR). The laboratory diagnosis of HAT is dependent on showing evidence of infection either by direct visualization of trypanosomes by microscope or by serological detection of antibody to trypanosomes in blood and csf (Fig. 7.7). Direct visualization of trypanosomes in blood is usually successful in the haemolymphatic stage of **T.b.r** because of the continuous parasitaemia, whereas it is difficult in **T.b.g** because of low or intermittent parasitaemia. Chancre aspiration and lymph node aspirate may be helpful when these are negative. Concentration methods including centrifugation are used to detect low levels of parasitaemia. The methods of direct

visualization involve examining the peripheral blood, the buffy coat, csf or rarely bone marrow for evidence of motile trypanosomes on a wet preparation or on Giemsa stain. In general the longer the duration of the illness the more difficult it is to find the organisms and the tests may have to be repeated in suspected cases more than once. The test of choice in suspected **T.b.g** infection is the antibody-detecting card agglutination trypanosomiasis test (CATT) which is easy to perform and widely available in endemic areas. Limitations include decreased sensitivity (87-98%) and specificity (93-95%).

CSF examination

It is critical to determine whether or not there is encephalitic involvement because to miss it and not to treat it results in the death of the patient. An LP is therefore indicated when encephalitis is clinically suspected and also in all cases of CATT positive tests as there are no reliable criteria for detecting exclusive early stage disease. It is performed only after one or two doses of suramin or pentamidine have been given in order to reduce the risk of parasites inadvertently entering the CSF from blood during the procedure. Direct evidence of encephalitis includes finding trypanosomes in centrifuged CSF either by direct visualization or by serology in the case of **T.b.g.** (Fig 7.7). Indirect evidence according to WHO includes lymphocytes >5 per ml and a raised protein in the CSF, although a cut off at a higher level of lymphocytes >20 per ml has been proposed to increase its diagnostic specificity. CT of brain is non diagnostic but may show non specific white matter changes and ventricular enlargement in long standing disease.

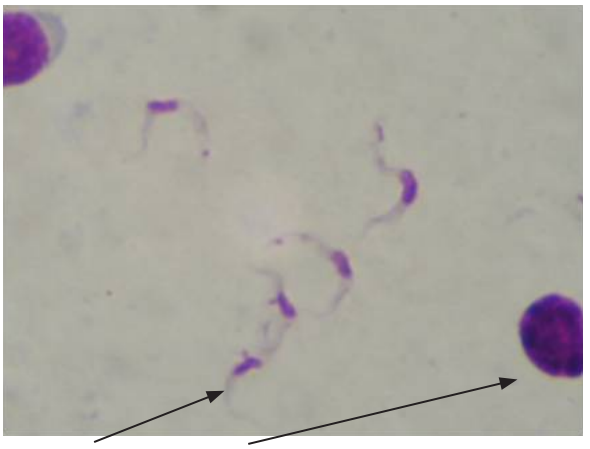


Figure 7.7 CSF in trypanosomiasis

Key points

- HAT occurs in two stages, haemolymphatic & encephalitic
- diagnosis: finding typical clinical & lab findings in pts from endemic area
- HAT confirmed by microscopy in T.b.r & by serology & microscopy in T.b.g
- LP indicated if encephalitis is suspected & in all CATT positive persons
- LP is done only after 1-2 doses of suramin or pentamidine

Treatment

The treatment of HAT is complex and toxic and must be closely monitored (Table 7.4). It is determined by the stage of the disease and whether it is ***T.b.r*** or ***T.b.g***. The early haemolymphatic stage of ***T.b.r.*** is treated with ***iv suramin*** and of ***T.b.g.*** with ***im pentamidine***. Allergy with suramin is uncommon (<1%) but can be fatal and a test dose is always administered before using it for treatment. Associated nephrotoxicity is usually reversible. This treatment is usually successful if the disease is confined to this stage. The late encephalitic stage of ***T.b.r*** and ***T.b.g.*** is treated with ***iv melarsoprol***. This is usually preceded by 1-2 doses of suramin to clear peripheral trypanosomes. In ***T.b.r melarsoprol*** is usually administered as a series of 3-4 cycles of 3 consecutive daily injections (Table 7.4) with a 7 day rest period between each cycle. The main danger is an acute reactive encephalopathy which occurs in 5-10% of treated patients, a half of whom die because of the drug, therefore just giving melarsoprol therapy has an overall fatality rate of 2.5-5%. *A new shorter 10 day course of iv melarsaprol at 2.2 mg/kg/daily may be effective for* ***T.b.g.*** Resistance to melarsoprol has recently been reported from the DRC. The concomitant use of steroids is controversial but there is evidence that their use may decrease the chance of developing the post-treatment encephalopathy particularly in ***T.b.g***. One steroid regime is dexamethasone 30 mg iv stat, and 15 mg q 6 hourly or prednisolone 1mg/kg po daily starting before the first dose and continuing through the last dose. ***Eflornithine (DFMO,)*** is a safer therapy than melarsoprol for late stage HAT but is only effective for disease caused by ***T.b.g***., being ineffective in the East African disease, ***T.b.r.*** However eflornithine is expensive and requires 2 weeks of continuous iv drug treatment in hospital. A combination of ***eflornithine infusion,*** for 7 days and the drug ***nifurtimox*** orally, for 10 days has been recently introduced (2009) and now appears to be effective primary therapy for ***T.b.g.*** It is not effective against ***T.b.r.***

Table 7.4 Drug treatment of human African trypanosomiasis

Drug	Type	Stage	Route	Dose/duration	Side effects
Suramin	T. b rhodesiense	Stage 1	iv	(5mg/kg test dose slowly iv on day 1). 20 mg/kg/iv (max 1 gm) on days 1,3, 5, 12, 19 & 26	allergy, anaphylaxis, renal failure, neurologic effects
Pentamidine	T. b gambiense	Stage 1	im	4 mg/kg im/od/ for 7–10 days	nephrotoxicity, hypoglycaemia low BP, site pain. nausea, leucopoenia
Melarsoprol (Mel B)	T. b rhodesiense & T. b gambiense	Stage 2	iv	3.6* mg/kg/od for 3 day cycles (series of 3-4 cycles)	acute reactive encephalopathy, neuropathy, diarrhoea and rash
Eflornithine	T. b gambiense	Stage 2	iv	100 mg/kg iv q 6hourly for 14 days in diluted normal saline/infused over 2 hours	leucopoenia, anaemia, diarrhoea and convulsions
Nifurtimox	T. b gambiense	Stage 1	po	15mg/kg /po/daily (5mg, 8 hourly) for 10 days	nausea, vomiting, abdominal pain, seizures, agitation tremor (neuropathy)

** different treatment schedules with doses ranging from 1.2 to 3.6 mg/kg/daily (in 3 divided doses) for consecutive 3 day cycles administered by slow iv injection, using a glass syringe and avoid leakage as it causes tissue necrosis. Total series of 3 to 4 cycles with a 7 day rest period between each cycle (see WHO recommendations),*

Key points

- Rx of early stage in ***T.b.r***. is with suramin & in ***T.b.g*** is with pentamidine
- Rx of encephalitic stage in ***T.b.r***. & ***T.b.g*** is melarsoprol or ***T.b.g*** eflornithine
- Rx of early & late stage ***T.b.g*** is with eflornithine & nifurtimox
- encephalopathy occurs in 5-10% of patients treated with melarsaprol
- 50% of patients with melarsaprol encephalopathy die

Prognosis

HAT is invariably fatal if untreated. It has been estimated that 20-30% of affected persons in endemic areas in Africa may die even with treatment either because of late diagnosis or inadequate treatment. The rate of relapse after treatment for the encephalitic stage is up to 20%. LPs are necessary every 6 months to confirm cure which cannot be assumed until after a 2 year follow up.

Prevention

HAT in Central and West Africa is prevented by active case finding through systematic community screening and passive clinical case finding and the treatment of all infected persons. In East Africa HAT is controlled by avoiding being bitten and by vector control through fly trapping and the clearing of riverine tsetse habitat.

Key points

- overall mortality in trypanosomiasis is high
- follow up is necessary after treated encephalitic stage and relapse is common
- prevention in ***T.b.g*** is by active case screening & passive case treatment
- prevention in ***T.b.r*** is by avoiding tsetse bites & by vector control

Table 7.5 Summary

	Gambiense (T.b.g)	Rhodesiense (T.b.r)
location	Central & West Africa	East Africa
reservoir	humans	cattle & wild animals
clinical presentation	sub-acute/chronic	acute
diagnosis	CATT/lymph node/CSF	blood film/CSF
management	pentaminine/eflornithine & nifurtimox	suramin/melarsoprol
control/prevention	case finding & treatment	avoid tsetse bites/vector habitat control

NEUROCYSTICERCOSIS

Neurocysticercosis arises from the larvae of the pork tapeworm *Taenia solium*. This tape worm is endemic in large parts of the world including large parts of Africa (Fig 7.8). It is estimated that over 50 million people worldwide are infected with cysticerci and it accounts for over 50,000 deaths annually. As many as 20 million persons in Africa may be infected. Around 10-40% of infected persons develop seizures and it is responsible for up to 30% of late onset epilepsy in endemic areas. It is the most common parasitic infection causing disease of the nervous system.

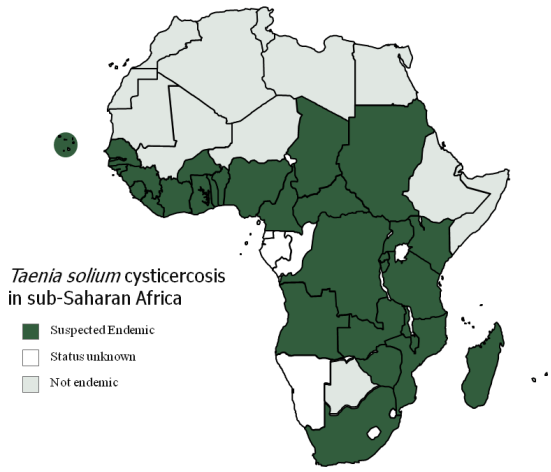
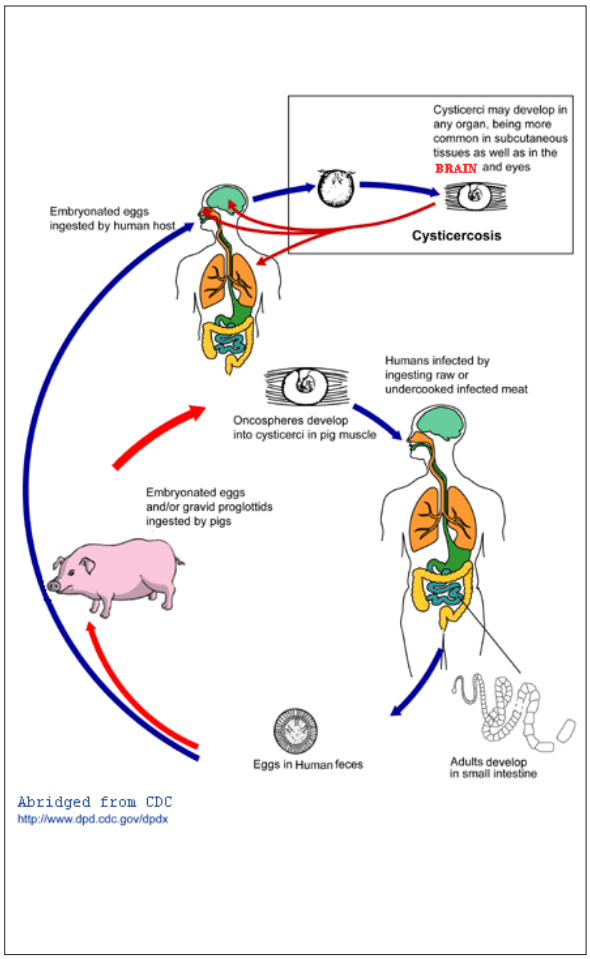


Figure 7.8 Map of cysticercosis distribution in Africa



Life cycle

Humans are the definitive hosts of the 2-4 meters long tapeworm that excretes viable ova in the stool. The pig is the intermediate host. Following ingestion of human faeces by the pig, ova migrate mainly to the pig's muscles and become larvae or cysticerci. Humans eat undercooked and measly pork containing the viable larvae. The life cycle is then complete when the larvae develop into an adult tapeworm in the small intestine of humans (Fig 7.9). However when humans accidentally become the intermediate host by ingestion of the ova through faecal-oral contamination from someone else's faeces or their own, the larval form may migrate and develop into cysts either in human brain or other organs, mainly muscles skin and eye. The most frequent source of ova is a symptom free tapeworm carrier in the household. Vegetarians and non pork eaters may thus acquire cysticercosis. About 15-25% of patients with neurocysticercosis will either have a past history of tapeworm or harbour a live one.

Figure 7.9 Life cycle cysticercosis

Pathology

Once in the brain, the mature larvae live dormant for 2-6 yrs and occasionally for 10 years or longer. These are known as cysticerci. They expand to 1-2 cms in size and eventually die causing the wall of the cyst to break down resulting in an intense local inflammatory reaction and later calcification. This cycle of pathology is responsible for the main clinical presentations including seizures. The clinical findings will depend on the site, number and stage of cysticerci. They occur in many tissues in particular, skin, muscle and brain. Typical skeletal muscles involved are those of the limbs and back. The main sites within the brain are the cortex, ventricles and subarachnoid space and infrequently the spinal cord.

Clinical Features

The most common clinical feature of neurocysticercosis is single or repeated seizures. These occur in >90% of cases. In endemic countries, including large parts of rural Africa neurocysticercosis is the most common cause of acquired epilepsy in adults. The cysts may infrequently cause focal neurological disorders; these include hemiparesis, hydrocephalus due to intraventricular cysts and rarely paraplegia (5%) due to spinal cord disease. The finding of hydrocephalus and raised intracranial pressure are an indication for shunting. There may also be evidence of cysts outside the CNS mainly in skin, muscle and eye (1-3%).

Diagnosis

The diagnosis is made mainly by a high index of clinical suspicion in a patient suffering from epilepsy coming from an endemic area. The diagnosis is supported by the finding of radiological evidence of cysts in muscle or brain. A radiograph of shoulder or thigh muscles may reveal typical calcifications following the planes of muscle fibres (Fig 7.10). A CT of head shows evidence of neurocysticerci (Fig 7.10), in particular their number, location and activity. However MRI is necessary to show intraventricular cysts or the racemose variety. The racemose variety of neurocysticercosis is seen on MRI as multiple thin walled cysts with the same signal as CSF and no central scolex (Fig 7.10). On CT cysts appear as small isolated or multiple lesions at the grey white matter junction or widespread throughout the brain. During this dormant phase after contrast, they appear as hypo dense cysts with little enhancement and a visible dot like central scolex (Fig 7.10). This is diagnostic of neurocysticercosis. In the later mature or dying cyst phase, they appear as ring enhancing cysts surrounded by an area of oedema. Older cysts may calcify and there may be hydrocephalus (Fig 7.10). Serological testing should be used together with results from neuroimaging to help establish the diagnosis. These include ELISA and enzyme immunosorbent/blot/assay tests on both serum and CSF. The tests may be negative in isolated cysts, but are usually positive where there are multiple cysts. However newer antigen and antibody based serological tests appear more sensitive to detect both active and inactive disease. The CSF is abnormal in about half the cases with elevation in white cells and protein. There may be an associated eosinophilia early on and also evidence of tape worm infection with eggs in the patient's stool in <20% of patients.

Treatment

The main indication for treatment is active parenchymal CNS disease. The suggested treatment for cysts is albendazole 15 mg/kg po daily for 10-28 days, although a higher dose of 30 mg/kg po daily has been used in patients with subarachnoid cysts. An alternative but less effective treatment is praziquantel 25mg/kg/po three times daily for 14-21 days (Table 7.6). There is controversy over the benefits and duration of treatment which ranges from 7 days to 3 months

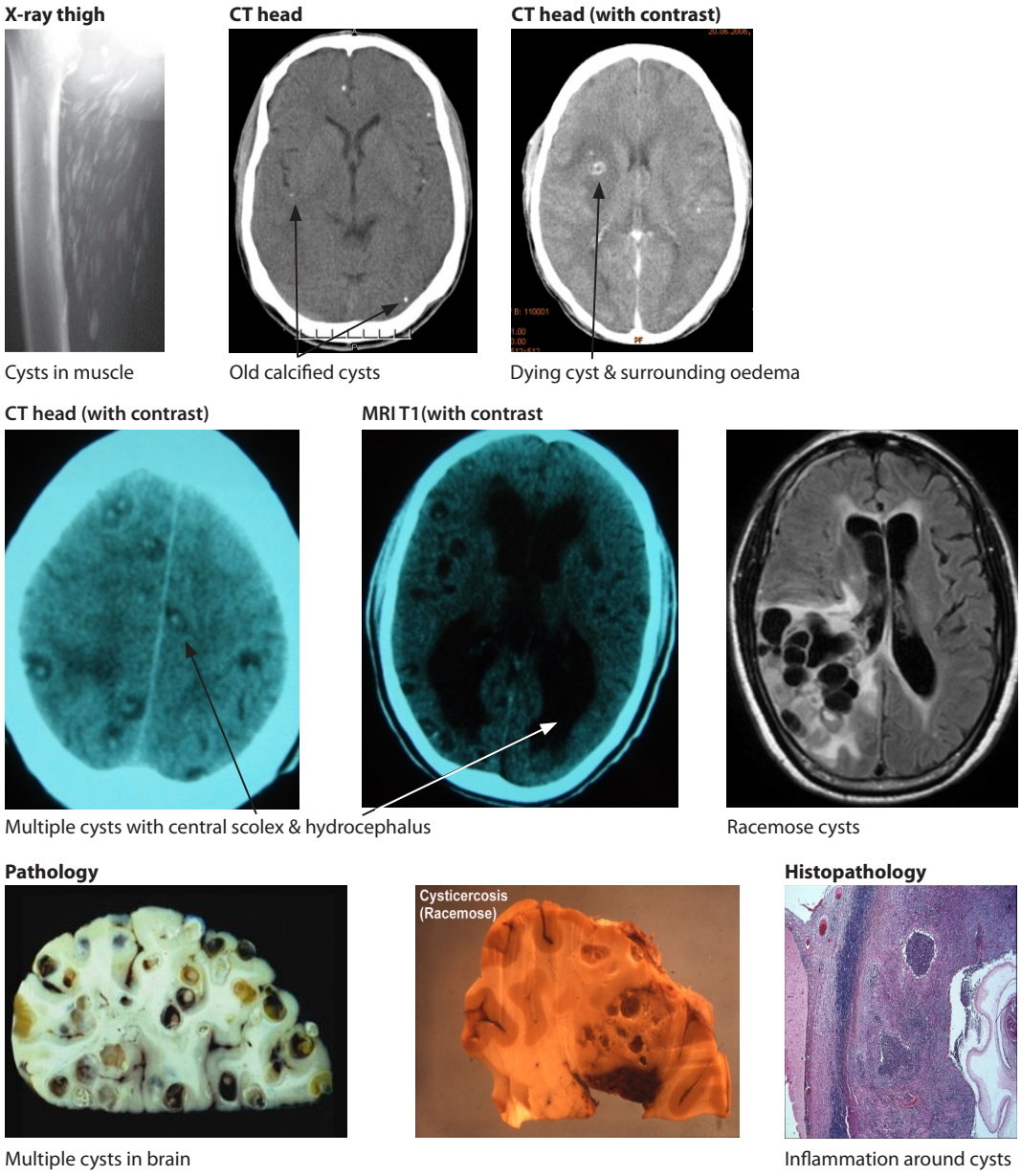


Figure 7.10 Muscle and brain in cysticercosis

or longer. In general the greater the cyst burden the longer the course of treatment. Cimetidine 400 mg tds given concurrently increases available blood levels of both anti parasitic drugs. Side effects of anti parasitic drug treatment include seizures, headaches and muscle enlargement. By starting treatment more cysts may die or die more quickly thereby causing more inflammation, oedema and consequently more headaches, seizures and sometimes encephalopathy.

This risk can be decreased by prescribing steroids. This is in the form of dexamethasone 0.4 mg/kg/po/daily (24 mg) or prednisolone 60 mg daily during active treatment. This is started

either a few days before or at the start of antiparasitic drug treatment and continued for at least 7 days throughout the treatment course or as long as symptoms e.g. headache persists. The presence of subarachnoid, intraventricular and too many intracerebral cysts are a relative contraindication to antiparasitic drugs because of danger of fatal encephalopathy. Neurosurgery in particular a shunt may be indicated for obstructive hydrocephalus which is mostly due to intraventricular forms of cysts blocking the ventricles. Seizures can be controlled with standard antiepileptic medications. The outlook in a single symptomatic cyst is excellent. However, the more malignant forms presenting with neurological deficits and coma have a grave prognosis with CFR rate of >50%.

Table 7.6 Drug treatment of Neurocysticercosis

Drug	route	Dose
albendazole	po	15 mg/kg/daily for 10-28 days
or		
praziquantel	po	25 mg/kg/tds for 14-21days
&		
dexamethasone	po	8 mg/tds for >7 days
or		
prednisolone	po	60 mg/daily for >7 days

Prevention

Neurocysticercosis is a largely preventable infectious disease. The main strategies for prevention include hygiene measures to interrupt direct person to person transmission. This involves potentially mass human chemotherapy to eliminate the tapeworm stage, improved human sanitation i.e. safe faeces disposal, pig husbandry and meat inspection.

Key points

- man is the definitive host of Taenia solium & excretes ova in faeces
- neurocysticercosis develops when humans ingest ova from human faeces
- epilepsy is the most common clinical manifestation
- diagnosis supported by serology & X-rays showing cysts in muscle & brain
- treatment is with albendazole 2-4/52 & steroids 1-4/52
- prevention: personal hygiene & mass Rx & safe, faeces disposal, pig husbandry & meat inspection

HUMAN SCHISTOSOMIASIS

Epidemiology

Schistosomiasis is caused by trematode flatworms (flukes) transmitted by snails. The disease is endemic in the tropics with an estimated 200 million people worldwide infected, 80% of whom are in Africa. The main species in Africa are *Schistosoma mansoni* and *S. haematobium*. *S. japonicum* is the main species in southeast Asia and China. Infection of the CNS is unusual in Africa but occurs in 2-4% of patients with *S. japonicum* infection.

Life cycle

Humans are infected by contact with fresh water, usually when working, playing or swimming. Cercariae, the larval form released from infected snails, penetrate the skin. The larval forms

then migrate and unite as pairs of mature worms with mansoni and japonicum living in the lower mesenteric veins (the intestinal form) and haematobium in vesical veins (the urinary form). They may live in the veins for up to 30 years but their usual life span is probably 3-5 years. Humans are the definitive host of the adult worms and excrete their eggs in either stool or urine depending on the type of infection. The snail is the intermediate host and miracidiae released from eggs coming from humans into water enter the snails and are later released as cercariae which in turn penetrate the skin and the life cycle is complete (Fig 7.11).

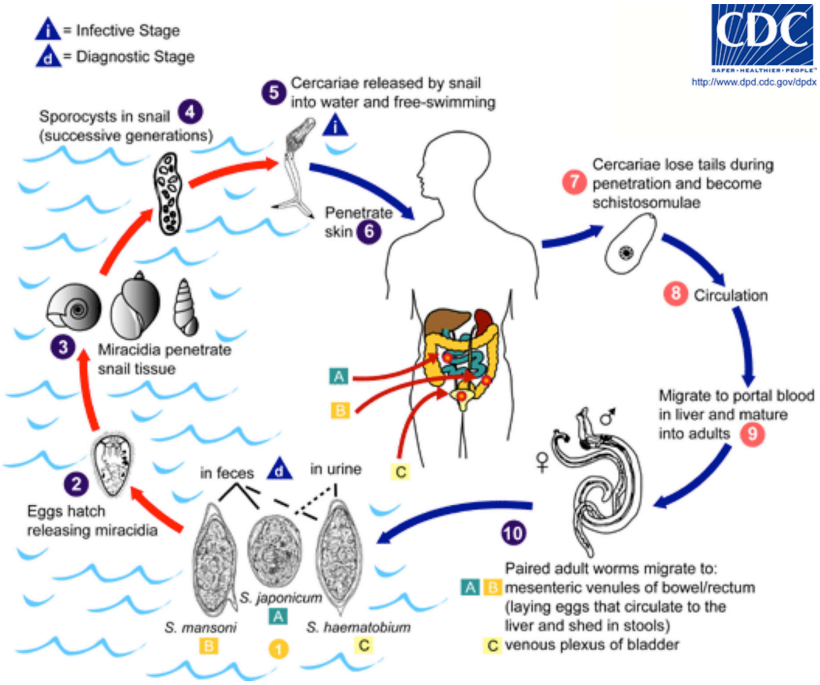


Figure 7.11 Life cycle schistosomiasis

Pathogenesis

The adult worms evade host immunity and some of their released eggs travel with the blood flow and get trapped in viscera and release antigens. This provokes a vigorous cell mediated inflammatory response particularly in early infection which forms intense granulomas around eggs, which gives rise to local pathology in the organ involved. The main sites for trapped *S. mansoni* and *S. japonicum* eggs are liver mainly causing portal hypertension and also the large intestine. *S. haematobium* eggs get deposited in the genitourinary tract causing bladder wall calcification, polyps, bladder stones and an increased risk of squamous cell cancer. The severity of systemic disease is proportional to the duration of worm infection and the egg load. When the eggs are deposited in the spinal cord or brain, this can lead to neurological disease. This can happen in two main ways, migration of egg laying worms to ectopic sites or embolization of eggs. Ectopic sites for worms include the inferior venacaval system with a right to left cardiac shunt or the paravertebral veins in the cord/cauda equina, or the cerebral cortical veins in the brain (Fig 7.12). Retrograde spread to the spinal cord from the inferior mesenteric veins through valveless pelvic veins is also a proposed mechanism for paraplegia. CNS involvement

is unusual in both *S. mansoni* and S. *haematobium*. Spinal cord disease accounts for >95% of all CNS disease in Africa. It occurs particularly in early infection with mansoni in the non immune host and when there is a heavy worm and egg load.

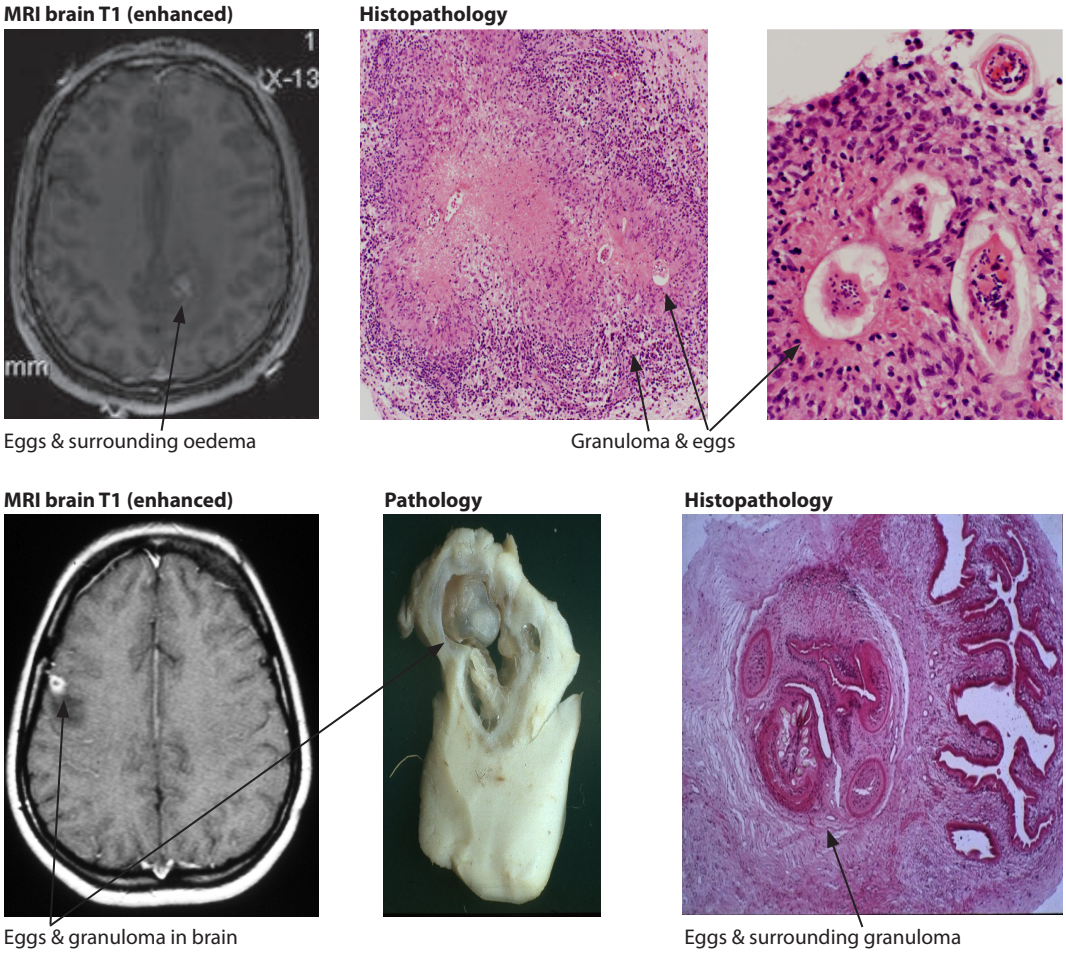


Figure 7.12 Brain in schistosomiasis

Clinical Features

The neurological findings occur as a result of eggs deposited in the spinal cord (lower end) or rarely in the brain. In the spinal cord, they cause a myeloradiculopathy which may result in paraparesis, mostly flaccid in type. Clinical features include low back pain, lower limb weakness, paraesthesia, bladder and bowel dysfunction and impotence. This is the most common neurological presentation of mansoni. Eggs in the brain present as space occupying lesions with focal neurological deficits, seizures and encephalopathy.

Diagnosis

The diagnosis is suggested by a previous or recent history of water exposure in an endemic area and confirmed by ELISA antibody tests or the demonstration of eggs in the stool by faecal smear or urine by sedimentation or filtration. Although an ELISA antibody test is less useful in endemic areas, a positive CSF test result (sensitivity <60%, specificity >95%) supports the diagnosis. CSF may show a mild elevation of cells and protein and slight decrease in glucose. Eosinophilia may be present especially early on in the disease. Neuroimaging requires MRI as CT is not sensitive for spinal cord disease. MRI shows enlargement of the lower end of spinal cord below T6 level usually involving T11-L1 with thickening of the nerve roots and cauda equina

Treatment

Patients with neurological disorders should be treated with praziquantel and steroids (Table 7.7). There is no consensus on the dose or duration of treatment and doses of praziquantel range between 40-60 mg/kg/po/daily for 1-14 days, although in suspected and confirmed cases a longer course is frequently used. Steroids should be used in the first instance for 2-6 weeks and sometimes continued for 3-6 months.

Table 7.7 Drug treatment of neuroschistosomiasis

Drug	route	Dose/duration
praziquantel	po	40-60 mg/kg/po/od 1-14 days
and		
methyprednisolone ***or*** **prednisolone**	iv po	15-20 mg*/kg/iv/od (max 1gm) 5-7 days 1.5 mg/kg/po/od for 3-6/52 and a tapering dose

** followed by oral prednisolone 1.5 mg/kg daily for 2-6 weeks*

Prognosis

The prognosis in treated spinal cord disease is good with 70% making a complete recovery. Recovery usually begins early within 1-2 days of starting treatment. The remaining patients are left with permanent deficits.

Prevention

The main methods of prevention involve regular intermittent mass drug treatment of exposed at risk populations usually school children with praziquantel, reduced contamination of water and a reduction or elimination of snails.

Key points

- neuroschistosomiasis is an uncommon complication of Schistosoma infection
- paraplegia is the most common neurological disorder & mostly occurs in the non immune host
- diagnosis is by serology & microscopic evidence of eggs & neuroimaging
- Rx is with praziquantel for 1-14/7 and steroids for 2-6 weeks
- secondary prevention: intermittent mass treatment of at risk populations with praziquantel
- primary prevention: reduced contamination of water & reduction or elimination of snails

HYDATID DISEASE

Echinococcosis in humans is mostly caused by the dog tapeworm *Echinococcus granulosus*. The dog is the definitive host and the adult tapeworm inhabits its intestine. Hydatid disease occurs, when humans come into contact with dog's faeces and the ingested ova develop into the cystic stage. The disease is estimated to affect 2-3 million people globally. It is endemic in large parts of Africa, mainly affecting the traditional cattle and sheep grazing communities. The prevalence in endemic areas ranges from 0.25 to 25%. Neurological involvement occurs in about 1-2% of cases.

Life cycle

The dog excretes the tapeworm eggs in its stool and these are accidentally ingested by grazing herbivores which then become intermediate hosts. These are mainly sheep, cattle and goats. The larval form penetrates the intestinal mucosa of the animal to lodge in the intestinal mesentery, liver and lungs, and develop into cysts. When the animal is killed the dog in turn ingests these organs which contain larval hydatid cysts. These larval cysts contain tapeworm heads or scolexes, which attach themselves to the intestinal wall of the dog and mature into the adult tapeworm and the life cycle is complete. Humans become accidentally infected by ingesting food or drink which has been contaminated by faeces containing ova from infected dogs. They then accidentally become the intermediate hosts (Fig 7.13).

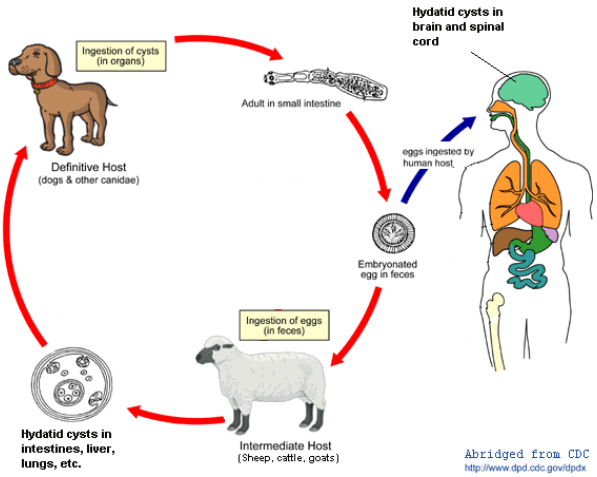


Figure 7.13 Life cycle Hydatid disease

Clinical features

Hydatid disease is characterized by slow growing cysts. It is a chronic disorder mainly of children and young persons but adults are also affected. The main sites are liver, lung but other organs may be involved. Neurological features depend on the site, age and maturity of the cysts. Cysts in the brain occur mostly in children and younger adults. They may be asymptomatic or present acutely with hydrocephalus, focal neurological deficits and seizures. Cysts in the spinal cord occur more in adults than children and present with paraparesis.

Diagnosis

The diagnosis is made by neuroimaging. CT reveals a striking large well defined rounded smooth thin walled unilocular, usually single cyst with mass effect. Calcification occurs in 20-40% of cases (Fig 7.14). Cysts may occasionally be multiple. The finding of a peripheral eosinophilia may be worrying as it may indicate that the hydatid cyst is leaking. Serology screening is not sensitive for extra hepatic involvement. The main differential diagnosis is between cystic brain tumours, an arachnoid cyst and abscesses.

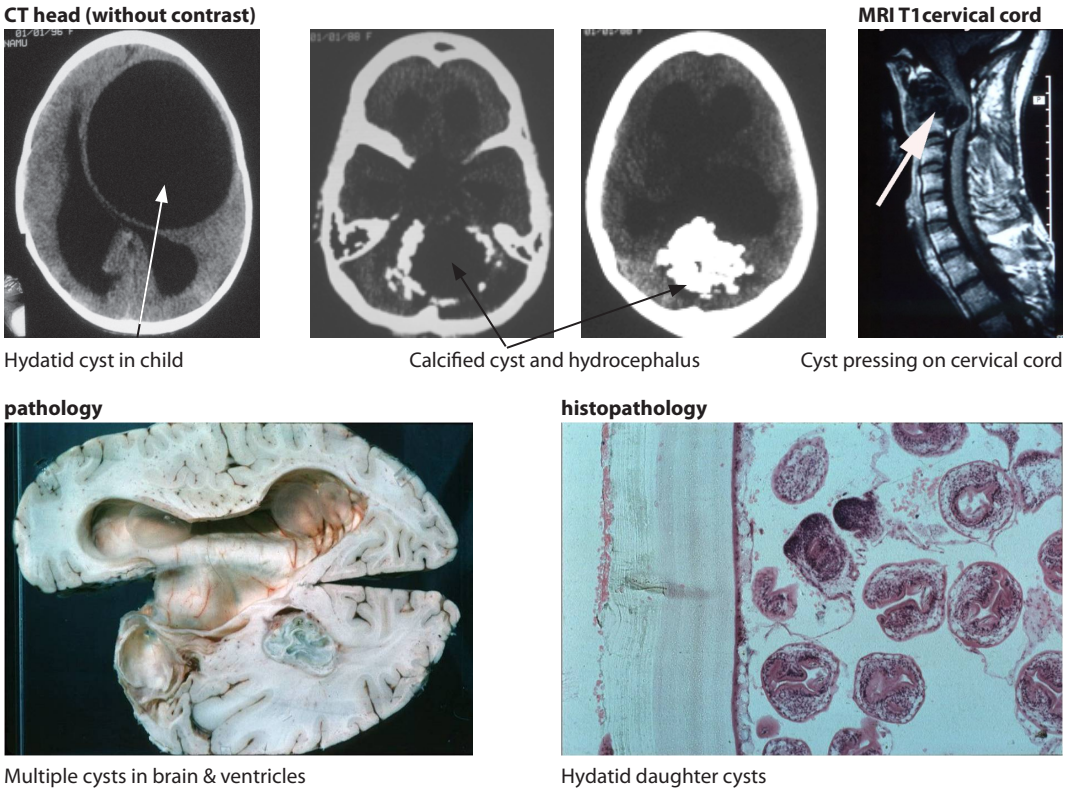


Figure 7.14 Brain and spinal cord in hydatid disease

Treatment

Management is both medical and surgical. Medical treatment is with albendazole alone or in combination with praziquantel. The recommended dosage of albendazole is 400 mg twice daily over a three or six month period. The optimum period of treatment remains uncertain. There is limited data on praziquantel but 40 mg/kg/week in combination with albendazole has been suggested and is the currently recommended treatment of choice. The advantage of two drugs is that while albendazole acts on the germinal membrane, praziquantel kills the proto-scolices or daughter cysts. The indications for medical treatment include multiple inoperable sites and to prevent secondary spread, and as an adjunct to surgery. Outcome with medical treatment is variable but clinical improvement and radiological resolution of cysts has been shown. Surgery is the management of choice for a lesion when there is symptomatic CNS involvement.

Prevention

Preventative measures in endemic areas include prophylactic dosing of dogs for tapeworm, avoiding feeding uncooked offal and raw meat to dogs and the regular inspection of meat for the presence of cysts.

Key points

- echinococcosis is caused by cystic stage of dog tapeworm
- humans infected when they accidentally ingest faeces from infected dogs.
- CNS disease occurs in 1-2% & includes hemiplegia, seizures & paraplegia
- diagnosis is by imaging showing cysts/Ca++ in the brain and spinal cord
- Rx: albendazole & praziquantel for >3/12 & surgery if symptomatic
- prevention: prophylaxis of dogs for tapeworm & inspection of meat for cysts

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