Schistosomiasis and the nervous system

The life cycle of the schistosome alternating between the snail and man.
INTRODUCTION

Schistosomiasis is one of the most widespread parasitic infections in man, second only to malaria in terms of socioeconomic and public health importance in many tropical and subtropical areas. It is particularly common in the rural areas of developing countries, with an estimated 200 million people infected globally, and 600 million exposed to infection. The prevalence of infection varies from under 10% in some areas to over 80% in others (Mahmoud 1977; Pitchford 1986).

It is caused by blood flukes (schistosomes), which invade the vascular system. The infection is transmitted by specific snails whose distribution determines the prevalence of the three different species of schistosome responsible for most disease in man: Schistosoma haematobium, S. mansoni, and S. japonicum (Table 1). S. haematobium is found mainly in Africa. S. mansoni has a similar distribution but in addition is endemic to South America, Japan and South-east Asia (Bird 1964; Warren 1986; Scrimgeour & Gajdusek 1985; Cosnett & van Dellen 1986; Davis 1996). S. haematobium mostly affects children aged 10–14 years, the rates rapidly falling after the age of 18. Infection rates of S. mansoni are very often higher than those of S. haematobium and do not fall as rapidly with age – it is most common in the age 10–24 years group. S. japonicum infections have no typical age distribution.

LIFE CYCLE

Schistosomes alternate between definitive hosts (mammals and birds) in which sexual reproduction takes place, and intermediate hosts (snails) in which asexual multiplication takes place (Warren 1978; Manson’s Tropical Diseases). On reaching fresh water, schistosome eggs (ova) from human faeces or urine release larvae (miracidia) that penetrate the soft tissues of susceptible snail species. The miracidia develop into cercariae, which leave the snail and enter the water. Cercariae penetrate human skin exposed to infested water. These then migrate to the liver via the lungs and transform into schistosomulae. The schistosomulae mature over many weeks and form mating pairs that pass to their final habitat within 4–13 weeks. The adult S. haematobium worms inhabit tributaries of the internal iliac vein around the bladder. In S. mansoni approximately 60% of the adult worms are found in the tributaries of the inferior mesenteric veins around the rectum, with
the remainder in the portal vein and liver. 40% of S. japonicum worms are found in the superior mesenteric veins and the rest again in the portal vein and liver. Adult female worms of S. mansoni and S. japonicum lay eggs that may be excreted in the faeces or carried via the portal circulation to the liver. Eggs of S. haematobium are generally deposited in the bladder wall and thence excreted in the urine. However, aberrations in the distribution of these worms are not uncommon. Therefore, S. mansoni and S. japonicum characteristically cause intestinal and hepatosplenic disease, whereas S. haematobium affects the urinary tract predominantly. The average period from cercarial penetration until the appearance of eggs is 50 days. Adult schistosomes may live for more than 10 years, and release between 300 and 3000 eggs daily.

Transmission of the disease depends on the distribution of the intermediate snail hosts, the extent of environmental contamination with human excreta, human water contact activities, and the host-parasite relationship in man, and in particular the role of protective immune mechanisms. Children are important as reservoirs of infection because of their indiscriminate excretory habits, particularly urination while swimming, and their opportunity for water contact in hot climates. Within an affected or at risk population there is only a small proportion of people with 'heavy' infections and typical symptoms. Most people have moderate or light infections with few or no symptoms. Non-immune visitors to endemic areas, or transients who become infected, often present with a more obvious clinical syndrome than residents of endemic zones.

**GENERAL ASPECTS OF SCHISTOSOMAL INFECTION**

Haematuria has been found in Egypt and Mesopotamia as far back as 1900 BC and calcified ova of the parasite have been found in the kidneys of two Egyptian mummies (1250–1000 BC). Theodor Bilharz established the relationship between the trematode worm and the disease that sometimes bears his name when he found the causal agent of S. haematobium in a mesenteric vein during a postmortem in 1851. Manson described the lateral spined eggs of S. mansoni in 1903. Infection by S. japonicum was recognized in the early years of the twentieth century in China, and the Philippines.

The clinical presentation of schistosomiasis occurs in three stages (Bird 1978; Boyce 1990).

- The first stage is caused by skin penetration by cercariae, which elicit a humoral response with pruritis and fever, and sometimes erythema and papules. But this seldom occurs in inhabitants of endemic areas, especially in Africa, and only rarely in non-immune visitors.
- The second stage of the illness (Katayama fever or acute toxaemic schistosomiasis) occurs at the time of ova production and deposition 3–6 weeks later. It is thought to be the result of an allergic response to the ova and is characterized by fever, eosinophilia, lymphadenopathy, diarrhoea, splenomegaly and urticaria. This acute illness is most marked in primary infections of nonimmune individuals.
- The third stage (chronic schistosomiasis) results from a delayed hypersensitivity reaction to the ova deposited in the tissues and is characterized by granuloma formation over a period of months to years. Eventually, the cumulative burden of parasite eggs in the intestinal wall, liver or bladder wall may cause obstructive uropathy, hydro nephrosis, pyelonephritis and renal failure in S. haematobium infection, and portal hypertension in S. mansoni and S. japonicum infection.

**PATHOGENESIS OF CENTRAL NERVOUS SYSTEM INFECTION**

Involvement of the central nervous system (CNS) is uncommon and the consequences depend on the spread and localization of ectopic eggs within the brain and spinal cord. (Scrimgeour & Gajdusek 1985; Pittella 1991). Neurological symptoms may occur during the early stages of the infection, during the slow progression to the chronic form, or concomitantly with the mild chronic forms. It is believed that the eggs reach the CNS through retrograde venous flow into the vertebral epidural venous plexus, which connects the portal mesenteric-pelvic venous system and venae cavae to the spinal cord and cerebral veins (Warren 1978; Liu 1993). Thus, eggs could enter the spinal veins under conditions of increased intra-abdominal pressure and reversed venous flow. Anomalous migration of the adult worms to spinal cord or cerebral leptomeningeal veins has been rarely reported but may explain why eggs can be concentrated just in one area of the CNS (Cosnett & van Dellen 1986).

Once the eggs are deposited in the nervous system, the mature larvae secrete antigenic...
and immunogenic substances, resulting in an inflammatory reaction that varies, according to the status of the host immune system, from an intense granulomatous reaction to very little reaction at all. In normal hosts with early peak reactivity to soluble egg antigens, large florid granulomas are formed. Conversely, in chronic schistosomiasis the granulomas tend to be relatively small compared with those formed shortly after the onset of oviposition. The reduction in responsiveness is due to a modulatory down-regulation of the host’s hypersensitivity to soluble egg antigen initiated by a subgroup of suppressor-inducer T-cells. More severe lesions tend to develop if there is a failure to modulate T-lymphocyte reactivity to schistosome antigens.

Asymptomatic deposition of eggs is more frequent than symptomatic infection, and is usually associated with advanced hepatosplenic and cardiopulmonary schistosomiasis. In these situations the eggs may have embolized to the brain via pulmonary arteriovenous shunts, or portal-pulmonary shunts (Wakefield et al. 1962; Bird 1978; Nash 1982; Scrimgeour & Gajdusek 1985). Eggs surrounded by granulomas frequently produce a mass effect. Vasculitis with secondary infarction may also occur (Pit-tella 1985).

CEREBRAL SCHISTOSOMIASIS

Cerebral schistosomiasis is rare considering the hugenumber of infected people. It is most commonly associated with S. japonicum infection, occasionally with S. mansoni and rarely with S. haematobium.

Cerebral involvement with S. japonicum infection

Yamagiwa first described an intracerebral granuloma caused by S. japonicum in 1899. The ova have a strong tendency to localize in the brain via pulmonary arteriovenous shunts, or portal-pulmonary shunts (Wakefield et al. 1962; Bird 1978; Nash 1982; Scrimgeour & Gajdusek 1985). Eggs surrounded by granulomas frequently produce a mass effect. Vasculitis with secondary infarction may also occur (Pittella 1985).

Cerebral involvement with S. mansoni and S. haematobium infection

The ova may be situated anywhere, but are mainly found in the cerebral and cerebellar cortex and leptomeninges. They are common in the brain of chronic fatal schistosomiasis, but are usually clinically silent (Gelfand 1950; Alves...
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Spinal schistosomiasis may occur during the early stages of infection, during the progression of the disease. Myeloradiculopathy is the most frequent form of spinal schistosomiasis. Although considered rare it may be under-reported. There are about 150 case reports and series in the literature against a background global prevalence of infection exceeding 100 million people (Ferrari 1999). The prevalence of oviposition in the spinal cord varies among studies, ranging from 0.3 to 13%. Many patients remain asymptomatic. Myelopathy occurs more commonly in S. mansoni infection, and almost never with S. japonicum infection (Scrimgeour & Gajdusek 1985; Cosnett & van Dellen 1986). In Africa most cases are attributed to S. haematobium infection (Wakefield et al. 1962; Bird 1964; Scrimgeour & Gajdusek 1985; Cosnett & van Dellen 1986). The disease may well be responsible for a proportion of patients with myelopathy of unknown aetiology in areas where schistosomiasis is endemic.

**PATHOLOGY**

Spinal cord and root disease may occur during the early stages of infection, during the progression to the chronic forms of human schistosomiasis, or concomitantly with the chronic forms (Ferrari et al. 2001). It is the consequence of ectopic schistosome ova with subsequent host reactions and tissue damage (Wakefield et al. 1962; Bird 1978; Nash 1982; Scrimgeour & Gajdusek 1985). Four pathological processes are responsible for the clinical features: myelitic, granulomatous, radicular and vascular. The first two are the most frequent. The radicular form may occur in association with the granulomatous form, but there is doubt about whether it occurs alone.

**The myelitic form** occurs when the tissue reaction results in necrosis, vacuolization and atrophy of the spinal cord with little or no granulomatous reaction around the eggs. This causes a rapidly progressive transverse myelitis with an unfavourable prognosis (Quieroz et al. 1979; Boyce 1990; Haribhai et al. 1991; Liu 1993). Acute or subacute transverse myelitis is probably under-recognized and under-reported compared with schistosomal mass lesions of the spinal cord.

**The granulomatous form** results from an intense granulomatous reaction around the eggs and is associated with gliosis and fibrosis. This leads to the formation of an intrathecal granulomatous mass that may be extra- or intra-axial (Wakefield et al. 1962; Scrimgeour & Gajdusek 1985; Cosnett & van Dellen 1986; Haribhai et al. 1991; Liu 1993). In most cases this mass is in the conus medullaris and presents as an expanding lesion. More rarely granulomas are found at higher levels in the cord (Quieroz et al. 1979). The prognosis is better than the myelitic form.

**The radicular form** is characterized by the presence of multiple granulomas on the surface of the spinal roots, particularly the roots of the cauda equina, producing a multiradiculare syndrome. The roots themselves may be thickened.

**The vascular form** is limited to a few cases, resulting from vasculitic occlusion of the anterior spinal artery or its branches and causing cord ischaemia (Siddorn 1978).

In practice, most cases have both medullary and radicular involvement, with varying degrees of necrosis, granulomatous and non-granulomatous inflammation, and vascular lesions consisting of new vessel formation, phlebitis, necrotizing arteritis, thrombosis and perivascular inflammation.

**CLINICAL FEATURES**

In most patients there are no other manifesta-
tions of schistosomiasis, except sometimes hepatosplenomegaly. From the clinical point of view the different pathological forms present similarly. Thus the patient is typically young, more frequently male, with no other complaints of schistosomal infection and presents with lumbar pain, often of a radicular nature, that is soon followed by rapidly developing weakness and sensory loss in the lower limbs associated with bladder dysfunction.

AGE AND SEX DISTRIBUTION
Schistosomal radiculomyelopathy occurs predominantly in young males living in rural areas. The age ranges from 14 months to 62 years, with a mean of 22 years. Most patients are 10–30 years old. The ratio of males to females is approximately 3:1. The predominance of males may be explained by their greater exposure in childhood, and later in the course of their work, to schistosome-infected water (Molyneux & Galatius-Jensen 1978; Cosnett & van Dellen 1986; Joubert et al. 1990).

INCUBATION AND ONSET
The time between onset and development of the full neurological syndrome varies from weeks to months, and rarely years (Wakefield et al. 1962; Bird 1964; Scrimgeour & Gajdusek 1985; Cosnett & van Dellen 1986; Liu 1993). Generally there is a short history, usually less than a month, with features suggesting a lower cord syndrome (Haribhai et al. 1991; Ferrari 1999). The neurological manifestations usually arise in an acute or subacute manner, with the signs and symptoms progressively accumulating and worsening. The features may also evolve more slowly, stabilize, and sometimes improve spontaneously, with later recurrence of the same and/or other manifestations following varying periods of time, usually days or weeks. About 40% of patients develop the full neurological picture within 1 week, 80% within 4 weeks, and 90% within 2 months. A few patients show a slower evolution over several months.

SYMPTOMS AND SIGNS
The early clinical manifestations consist of lumbar and/or lower limb pain, lower limb muscle weakness, paraesthesiae and hypoesthesia, and bladder dysfunction (Cosnett and van Dellen 1986; Haribhai et al. 1991; Liu 1993; Ferrari 1999). There may be signs of meningeal irritation. The low back pain can be severe at the onset and may radiate into the saddle area or lower limbs. Lower limb weakness is present in practically all patients, usually it is severe, and it may be symmetrical or asymmetrical. Most patients develop a flaccid paraparesis, or paraplegia and areflexia. The level of the lesion in patients with a granuloma is most commonly T12 to L1, although a level above or below this may occur. Flaccid quadriplegia is a rare presentation of bilharzial myelopathy (Molyneux & Galatius-Jensen 1978). When higher levels of the spinal cord are affected, there may be spasticity and extensor plantar responses.

Sensory disturbance is common but often overshadowed by the motor weakness. There is variable sensory loss in the sacral and lower lumbar dermatomes and all modalities of sensation may be affected. Pain and paraesthesiae in the lower limb are also common, usually in a radicular distribution. The sensory changes may be either symmetrical or asymmetrical, and may vary during the course of the disease. Most patients with an myelitic presentation have a clear sensory level at or below T10, and occasionally at the mid thoracic or cervical level.

Severe bladder dysfunction is often an early feature with urinary retention, a flaccid distended bladder and overflow incontinence. Lesser degrees of bladder disturbance may occur. Bowel dysfunction may also be present, and sexual dysfunction is probably common although it has not often been reported.

In summary, the physical signs in the granuloma group reflect a patchy, incomplete and often asymmetrical involvement of the conus and cauda equina, with striking motor disturbance and often less sensory disturbance. In contrast, the myelitic group is more likely to have a paraplegia with a crisp sensory level. However, the distinction between these two types is not always so clear cut.

INVESTIGATIONS
Eosinophilia is the only haematological abnormality and, although nonspecific, is present in about 65% of patients (Liu 1993).

The cerebrospinal fluid
In most patients there is an increase in the CSF total protein and/or a pleocytosis (Scrimgeour & Gajdusek 1985; Cosnett & van Dellen 1986; Haribhai et al. 1991; Liu 1993). The number of cells varies from 6 to usually less than a 100 per cubic millimeter, mainly lymphocytes. In a few patients neutrophils predominate. Eosinophils are detected in less than half the patients but...
this can contribute to the diagnosis because its most frequent cause is helminthic infection of the nervous system. The total protein concentration usually ranges from 0.5 to 1.8 g/L. Occasionally xanthochromia is detected, reflecting spinal block. Glucose levels may be normal or slightly depressed.

**Imaging**

Myelography, CT-myelography and MR imaging may reveal an expanded lower spinal cord or conus with or without CSF block, but in the myelitic form there may be few or no changes (Cosnett & van Dellen 1986; Joubert et al. 1990; Haribhai et al. 1991) (Figs 1–3). Thickening, matting and irregularity of the roots of the cauda equina is also common. Atrophy of the spinal cord may be found in longstanding cases. Abnormalities may be present on MRI when none are present on myelography or on CT-myelography. MRI may show diffuse hyperintensity of the conus and distal thoracic cord on T2 weighted images, and expansion of the

![Figure 1](image1.png)  
**Figure 1** Sagittal T1 weighted MR scan of the spine with gadolinium enhancement. There are multiple nodular enhancing lesions in and around the lower cord and conus (arrow).

![Figure 2](image2.png)  
**Figure 2** Axial T1 weighted MR scan with gadolinium enhancement showing a hyperintense lesion in the left anterior part of the conus (arrow).

![Figure 3](image3.png)  
**Figure 3** Axial T1 weighted MR scan with gadolinium enhancement showing multiple hyperintense nodular lesions in the region of the conus (arrow).
distal cord or conus on T1 weighted images. T1 weighted sagittal images with contrast show a patchy heterogeneous enhancement with areas of more intense focal nodular or multinodular enhancement. There may also be enhancement of the roots of the cauda equina. Although suggestive, these alterations are not specific (Table 3) (Silbergleit & Silbergleit 1992; Blunt et al. 1993; Grand et al. 1996; Liu 1996; Murphy et al. 1998; Van Leusen & Perquin 2000).

**Search for schistosoma eggs in biological specimens**

Schistosomal eggs are detected in the faeces, urine or tissues (rectal mucosa, bladder mucosa, skin or medullary tissue) in over 80% of patients (Scrimgeour & Gajdusek 1985; Cosnett & van Dellen 1986; Haribhai et al. 1991). Difficulty in detecting eggs in urine and/or faeces is not uncommon. S. haematobium ova are more likely to be detected in the urine, especially if centrifuged, whereas in the case of S. mansoni, biopsy of the rectal mucosa is more likely to confirm the infection. Ova may also be found in the stools. S. haematobium, however, is also frequently found on rectal biopsy. In young children, scrapings from the rectal mucosa are preferable to rectal biopsy. Some patients show dual infection with S. haematobium and S. mansoni. Where both species are endemic, recovery of one species from urinary faeces does not prove it is the cause of the myelopathy.

**Immunodiagnosis**

The search for serum antibodies against schistosome infection has limitations, mainly due to cross-reactions with antigens of other organisms, particularly helminths, and to the difficulty in distinguishing between active and previous infections. The ELISA test using specific egg antigens has superseded previous serological tests (Cosnett & van Dellen 1986; Haribhai et al. 1991; Pammenter et al. 1991; Ferrari et al. 1995). Antibodies are positive in over 90% of patients. Although this finding is evidence of exposure to the helminth, it does not mean the patient has the disease, and so is of greater value in patients who do not reside in an endemic area. A negative test does not, however, completely rule out a schistosomal aetiology of myeloradiculopathy. It is also useful to take into consideration the level of the anti-schistosomal egg IgG antigen. A value below 0.1 µg/mL practically excludes the diagnosis, whereas a value above 1.4 µg/mL more or less confirms the diagnosis (Ferrari et al. 1993).

The detection of antibodies in the CSF may be more useful as their presence indicates diffusion of immunoglobulin molecules across an injured blood–brain barrier and/or local synthesis of antibody by immunocompetent cells that have gained entry into the CNS. In neuroschistosomiasis there is an inflammatory response with mild to moderate impairment of the blood–brain barrier and intrathecal synthesis of antibodies. In the CSF anti-schistosomal antibodies may be detected in over 80% of patients when tested by different techniques, predominantly ELISA and indirect immunofluorescence. Numerous authors consider a positive result to be a sign of intrathecal schistosomal infection. Others interpret this finding merely as evidence of exposure to the helminth.

**DIAGNOSIS**

Short of laminectomy and biopsy, the diagnosis is based on circumstantial evidence. Nevertheless, the clinical picture is so characteristic that if the patient has had likely exposure to the parasite, there are few other diagnostic possibilities even though the clinical signs and symptoms are not specific. The diagnosis of schistosomal transverse myelitis is more difficult to establish than that of granulomatous lesions of the conus or cauda equina.

Therefore, the diagnosis is usually based on:

- Characteristic lumbar or lower thoracic spinal cord symptoms.
- Evidence of exposure to schistosomes - the

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*Table 3: Differential diagnosis of schistosomal myelopathy*

| Tuberculoma and tuberculous arachnoiditis |
| Cysticercosis |
| Syphilis |
| Metastatic neoplasia |
| Lymphoma |
| Ependymoma |
| Epidural abscess |
| Intraspinal haemorrhage |
| Vascular occlusion |

When the level of the lesion is higher than the lower dorsal cord, the differential diagnosis becomes broader and includes viral myelitis, multiple sclerosis, and HTLV-1 myelopathy. Gnathostomiasis, paragonimiasis and echinococcosis can rarely cause spinal cord disease.
demonstration of ova in stool or urine, or in material from rectal or liver biopsies. Although the detection of schistosome antigens in serum or CSF is useful, it does not differentiate between active infection and past exposure.

- Exclusion of other causes of transverse myelitis, most of which affect the midthoracic cord (Table 3).

The absence of intestinal, hepatic, or bladder disease does not exclude the diagnosis. The presence of eosinophils in the CSF and expansion of the conus or of the lower spinal cord are suggestive of schistosomal myelopathy, but are not specific, especially in endemic areas. An obvious further difficulty in underdeveloped rural areas is the lack of sophisticated investigative facilities for excluding other causes of spinal cord damage.

Physicians in non-endemic areas may encounter schistosomiasis in immigrants or travellers from endemic areas, and are likely to see more cases in the future because of ongoing immigration, and burgeoning international air travel and tourism.

**TREATMENT**

Due to the large number of variables it is difficult to assess what constitutes optimal treatment, and the natural history of the disease is still not fully understood. Stabilization or even spontaneous improvement may occur without treatment.

Praziquantel is the drug of choice for the treatment of all forms of schistosomiasis and may have immunosuppressive and anti-inflammatory actions as well as being ovicidal (King & Mahmoud 1989; Chandra Shekhar 1991; Haribhai et al. 1991). A commonly used dosage regime is 60 mg/kg/day for 3 days, with prednisolone 1.5–2.0 mg/kg/day for 3 weeks and then tapered off over several weeks. More prolonged treatment with praziquantel may be required in some patients. By destroying the adult worm, praziquantel interrupts oviposition. Following treatment with praziquantel and corticosteroids there is usually rapid clinical improvement, often within days, but usually by 6 weeks (Scrimgeour & Gajdusek 1985; Haribhai et al. 1991). There is a parallel improvement in the CSF pleocytosis and chemistry, and in the laboratory and radiological profiles.

Praziquantel is well tolerated. Minor adverse effects include epigastric or abdominal discomfort, nausea, anorexia and diarrhoea. Headache, pruritis, fever, dizziness, fatigue and transient skin eruptions may also occur.

Corticosteroids can reduce or limit the compression and destruction of the nervous system by their anti-inflammatory and immunosuppressive properties. Patients may even show a dramatic improvement after the introduction of corticosteroids alone. Although there have been no controlled trials, it is common practice to administer corticosteroids with praziquantel.

Other drugs include oxamniquine and metrifonate for *S. mansoni* and *S. haematobium*, respectively, but they have been superseded by praziquantel.

Surgical decompression is not urgently needed when the diagnosis is very likely. It should probably be reserved for those who deteriorate despite medical treatment, for diagnostic purposes, and possibly for patients who develop acute paraplegia with CSF block (Scrimgeour & Gajdusek 1985; Liu 1993).

Because spinal schistosomiasis is seldom associated with clinical evidence of hepatosplenic schistosomiasis, the diagnosis may not be made in time to prevent irreversible spinal cord damage. Therefore, if schistosomal myelopathy is suspected, treatment with praziquantel should not be delayed until the results of diagnostic tests are available. This is particularly important in rural areas while the patient awaits transfer for investigation.

**PROGNOSIS**

Mortality in confirmed cases has fallen from about 72% prior to 1965 to 12% as of 1985 (Scrimgeour & Gajdusek 1985). Early treatment is more likely to be associated with a favourable outcome, and conversely lack of recovery may be due to delayed treatment. Nevertheless some patients, even when treated adequately in the early stages, do not recover at all. Approximately 70% of patients show full or partial recovery. Patients with necrotic myelitis do worse, probably because of irreversible structural cord damage, or due to delayed diagnosis and treatment.

**REFERENCES**


