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Neuroschistosomiasis

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Schistosomiasis is an infection caused by digenetic trematode platyhelminths of the genus *Schistosoma*. These blood flukes use man and other mammals as definitive hosts and aquatic and amphibious snails as intermediate hosts. Of the schistosomal species, *S. mansoni, S haematobium* and *S. japonicum* are the most important to man and the most widely distributed. The infection affects about 200 million individuals in 74 countries of Latin America, Africa and Asia. Far less commonly, schistosomes reach the central nervous system (CNS). This may occur at any time from the moment the worms have matured and the eggs have been laid. For this reason, CNS involvement may be observed with any of the clinical forms of schistosomal infection. The presence of eggs in the CNS induces a cell-mediated periovular granulomatous reaction. When eggs reach the CNS during the early stages of the infection or during evolution of the disease to its chronic forms, large necrotic-exudative granulomas are found. In-situ egg deposition following the anomalous migration of adult worms appears to be the main, if not the only, mechanism by which *Schistosoma* may reach the CNS in these stages. The mass effect produced by the heavy concentration of eggs and the presence of large granulomas in circumscribed areas of the brain and spinal cord explains, respectively, 1) the signs and symptoms of increased intracranial pressure and focal neurological signs; and 2) the signs and symptoms of rapidly progressing transverse myelitis, usually affecting the lumbosacral segments of the spinal cord. Most of the cases of CNS involvement associated with the hepatosplenic and cardiopulmonary chronic forms, or with severe urinary schistosomiasis, though more frequent, are asymptomatic. In the patients with these clinical forms, the random and sparse distribution of eggs in the CNS indicates that the embolization of eggs from the portal mesenteric system to the brain and spinal cord constitutes the main route of CNS invasion by *Schistosoma*. The discrete inflammatory reaction elicited by the sparsely distributed eggs in the CNS explains the lack of neurological symptoms that could be produced by egg deposition.

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Introduction

Schistosomiasis is an infection caused by digenetic trematode platyhelminths of the genus *Schistosoma*. These blood flukes use man and other mammals as definitive hosts and aquatic and amphibious snails as intermediate hosts. Five schistosomal species are important to man; *S. mansoni, S. haematobium* and *S. japonicum* are the most widely distributed, whereas *S. intercalatum* and *S. mekongi* occur only in a few countries of West and Central Africa and in the Mekong Delta (Laos and Cambodia), respectively (124). Two other species, *S. mattheei* and *S. bovis*, may be infective to man. *S. bovis* infection is rare and occurs in Central and Southern Africa, whereas *S. mattheei* is frequent in Southern Africa (124). The development of *S. mattheei* in man depends on the presence of *S. haematobium* and *S. mansoni*, and hybridization is seen to occur between *S. haematobium* and *S. mattheei*. Since all reported cases of involvement of the central nervous system (CNS) in schistosomiasis are attributed to *S. mansoni, S. haematobium* or *S. japonicum*, [respectively, neuroschistosomiasis mansoni (NSM), neuroschistosomiasis haematobia (NSH), and neuroschistosomiasis japonica (NSJ)], only infection by these three main species will be considered here.

S. mansoni, S. haematobium and *S. japonicum* differ from each other in a number of ways, such as the time between penetration in man and oviposition, arrangement of reproductive organs, fecundity, egg shape and size, location of intravascular habitat in the human host, and specificity of the intermediate host. These differences explain, to a large extent, the various clinical forms found in infected individuals.

Epidemiology

Schistosomiasis is endemic in 74 countries of the world (128). The total number of individuals infected with *Schistosoma* in these countries is estimated to reach 200 million, and another 600 million are exposed to the risk of infection. Parasitism by *S. mansoni* affects approximately 110 million individuals living in Brazil (part of the northeast and southeast regions), Suriname, Venezuela, several Caribbean islands, Egypt, most of the countries in the west, equatorial and central-south parts of Africa, and the Arabian Peninsula. Approximately 90 million individuals in most of the Africa and Middle East countries are infected with *S. haematobium*. In China, Indonesia, the Philippines and Thailand, infection by *S. japonicum* is estimated to affect almost two million people. In Japan, no new cases of schistosomiasis have been reported since 1978.

Schistosomiasis is found predominantly in rural and agricultural areas, though in some countries it is also seen to occur in the periphery of urban centers. Water contamination by human excreta and snail infection are favored, in these endemic areas, by the inadequate hygienic practices and poor sanitary conditions commonly found among the populations. The collection and storage for domestic use of water from contaminated sources, combined with contact with infested waters during recreational or work activities, also prevents eradication of this parasitosis. Over the last few decades, schistosomiasis increased its geographical distribution and its prevalence in some endemic areas. This is attributed, among other factors, to the building of dams and irrigation systems, which have provided additional habitats for the intermediate hosts. Also, with infected individuals continuously migrating to nonendemic areas, the parasite tends to adapt to new species or strains of snails. Massive movement of populations became common in recent years due to drought, famine and tribal and civil wars in different parts of Africa and the Middle East. This intensive migration should be regarded equally as a potential cause of increased transmission of schistosomiasis in these areas (64). In addition to being found in the populations of these endemic areas, schistosomal infection may also be detected in immigrants from these areas, as well as in residents of countries where schistosomiasis does not occur but who became infected while traveling or temporarily residing in locations where the parasitosis is endemic.

Life Cycle of Schistosoma

The life cycle of *Schistosoma* commences with the parasite eggs being excreted in the feces (*S. mansoni, S. japonicum*) or in the urine (*S. haematobium*) of infected individuals (84, 124). The shape and size of schistosomal eggs vary from species to species. *S. mansoni* and *S. haematobium* eggs are of a rather symmetric oval shape, with a lateral (*S. mansoni*) or terminal (*S. haematobium*) spine, and vary from 112 to 174 µm in length by 40 to 70 µm in width. When the spine cannot be visualized, the eggs of these two species can be differentiated using the Ziehl-Neelsen stain procedure: the shell of *S. mansoni* eggs takes on a bright red color (acid fast), whereas that of *S. haematobium* eggs does not stain. *S. japonicum* eggs are round-shaped, vary from 70 to 100 µm in length by 50 to 65 µm in width, and possess a reduced lateral spine.

On encountering clean fresh water, adequate light and temperature around 28°C, the mature eggs hatch into ciliated embryos, known as miracidia, which swim freely until they find the intermediate host (aquatic snails of the genus *Biomphalaria* and *Bulinus*, carriers of *S. mansoni* and *S haematobium*, respectively, and amphibious snails of the genus *Oncomelania*, carriers of *S. japonicum*). Within the snails, the miracidia develop into primary sporocysts followed by secondary sporocysts produced from the multiplication of the germinative cells of the miracidium. After migrating to the lymph vessels around the hepatopancreas of the snail, the secondary sporocysts change into cercariae - larvae with a forked, elongated cylindrical tail - which are infective to man. After releasing itself from the snail, the cercaria swims freely and, upon finding the definitive host, penetrates into its skin. For this, it utilizes proteolytic enzymes secreted by its acetabular glands. During the penetration process, the cercariae lose their tail and change into schistosomula, which then move through the cutaneous blood and lymph vessels to the right heart and lungs. After remaining in the lungs for several days, they migrate via the bloodstream or directly through the pleural or diaphragm tissues to the intrahepatic system. The schistosomula remain in the intrahepatic branches of the portal vein until they grow into adult male and female schistosomes, mate, and pass down into 1) the smaller branches of the inferior mesenteric vein, specially at the level of the sigmoid colon and rectum submucosa (*S. mansoni, S. japonicum* and, to a lesser degree, *S. haematobium*); 2) the venules of the pelvic plexuses, in particular of the vesical plexus (*S. haematobium*). Here, the worms begin laying the eggs, and the biological cycle of the parasite commences again.

The eggs, in a still immature condition, are deposited within small venous vessels. During the passage of the eggs through the intestinal and vesical wall, the embryos reach full maturity, a process that lasts 6 to 7 days. An adult female *S. mansoni* lays about 100 to 300 eggs per day; a *S. haematobium* female, from 20 to 200 eggs per day; and a S. *japonicum* female, approximately 500 to 3500 eggs per day. Of these, 25 to 30% are excreted in the feces and in the urine, the remainder being trapped in the intestinal and vesical wall and carried in the circulation to the liver and other organs. The time between pene-

tration of the cercariae in man and the passing out of eggs from the body varies from 42 to 56 days (*S. mansoni*), from 60 to 90 days (*S. haematobium*), and from 29 to 42 days (*S. japonicum*).

Schistosomes may reach the CNS at any time from the moment the worms have matured and the eggs have been laid. For this reason, the presence of these parasites may be observed with any of the clinical forms of schistosomal infection (103). Sparse or massive embolization of eggs from the portal mesenteric and pelvic system may occur (41,106,120): 1) through previously developed pulmonary arteriovenous shunts (61,122), or portopulmonary anastomoses via the azygos vein (18,123) allowing the eggs to reach the pulmonary veins and be carried through the left heart into the arterial system, or; 2) through retrograde venous flow (41) into Batson's vertebral epidural venous plexus (11), which connects the portal venous system and venae cavae to the spinal cord and cerebral veins. The presence of portal hypertension in patients with hepatosplenic schistosomiasis (*S. mansoni* and *S. japonicum*) apparently causes these anastomoses to open up more easily. Another possibility is the anomalous migration of adult worms, through the above described routes, to sites close to the CNS, followed by in-situ egg deposition. Prepostural lesions related to the migration of schistosomula are not known and are unlikely to occur, as the CNS is not within the usual route followed by the immature worm.

Pathogenesis

The pathogenesis of the CNS lesions produced by *S. mansoni, S. haematobium* and *S. japonicum* depends basically on the presence of parasite eggs and the host immune response. As far as *Schistosoma* eggs are concerned, the glandular secretion produced by the mature miracidium is known to contain antigenic and immunogenic substances that account for the periovular granulomatous reaction. Separately neither the egg shell nor the miracidium can produce granulomas. The embryos contained in the eggs do not reach maturity until 6 to 7 days after egg deposition by the female worm. The miracidium remains viable for approximately 12 to 15 days, and it is during this period that the soluble egg antigens disseminate through the pores in the shell. Among these soluble egg components are the glycoproteins that induce the granulomatous reaction, some of which have been purified, such as the major serologic antigens (MSA1, MSA2, MSA3) and the major egg glycoprotein (MEG), obtained respectively from the Puerto Rican (95) and the Egyptian (76) strains of *S. mansoni*; the major antigenic egg glycoproteins obtained from the Egyptian strain of *S. haematobium* and the Chinese strain of *S. japonicum*; and the 140 kDa egg glycoprotein obtained from the Japanese strain of *S. japonicum*. Within 18 to 21 days the miracidium dies, is phagocytized and removed by the macrophages, only its shell remaining. Complete calcification of the egg, observed more frequently in *S. haematobium* and *S. japonicum* infection, is also possible.

The granuloma formed around the egg probably affords protection to the host by sequestering antigens secreted by the miracidium. The cell-mediated periovular granulomatous response is specific for soluble egg antigens. In murine schistosomiasis, it appears to be mediated predominantly by CD 4^+ Th2 cells (58,62,127,130), although interaction with Th1 and Th0 cells is also involved (26,29,134). The immune response to the antigens released from the eggs reaches maximum intensity in the early stages of the infection, leading to the formation of large necrotic-exudative granulomas. At this stage, lymphokine secretion is maximal and coincides with the strong granulomatous reaction. Interleukin-2 (via the generation of Th2-associated responses), interleukin-4 and interleukin-5 appear to increase granuloma formation, whereas interferon gamma may downregulate interleukin-2 and interleukin-4 production and, therefore, the corresponding granuloma formation (25,26,65,75,130,131,133). Different soluble egg antigen fractions elicit distinct lymphokine responses: predominant interferon gamma and interleukin-2 production is elicited by the 32-kDa fraction, whereas the 35- and 38-kDa fractions elicit predominant interferon gamma and interleukin-4 production (74). These data support the notion of a cross-regulatory network of lymphokines and also show that granuloma formation and its modulation are highly complex events involving both Th2 (interleukin-4 and interleukin-5) and Th1 (interleukin-2 and interferon gamma) lymphokines. As infection progresses from the acute to the chronic phase, the cell-mediated anti-soluble egg antigens responses become attenuated in a process known as modulation (14). In the chronic phase, lymphokine production diminishes and the granulomatous response is downmodulated. This process is due to the inhibiting effect of suppressor T lymphocytes (98). The modulating-suppressing effect on the granuloma appears to be exerted by inductor-suppressor and effector-suppressor factors produced by suppressor T lymphocytes.

In addition to the presence of parasite eggs and host immune response, two other important aspects should be considered in the pathogenesis of NS: the route by which schistosomes reach the CNS and the clinical forms of the disease that are associated with CNS involvement. In the large majority of NS cases in which neurological symptoms are present, involvement of the CNS starts (103); 1) in the early stages of infection, while the patient is still asymptomatic (inapparent acute form); 2) during the slow and gradual evolution of the disease to its chronic stages, or; 3) concomitantly with the chronic intestinal, hepatointestinal and mild urinary (without obstructive uropathy) forms. The anomalous migra-

tion of adult worms to sites close to the CNS followed by in-situ egg deposition appears to be the main, if not the only, manner by which NS associated with any of the above mentioned clinical forms may be acquired (103). This claim is supported by; 1) the occasional finding of adult worms in the lumen of spinal cord leptomeningeal veins (*S. mansoni*) and choroid plexus vessels (*S. haematobium*) (28,36,55); 2) the preferential lodging of eggs, in the cases of spinal cord NS, in the lumbosacral and inferior thoracic regions, with the highest segments of the spinal cord and brain being preserved in practically all the cases; 3) the involvement of circumscribed cerebral areas, such as the parietal and occipital lobes and the cerebellum, in patients with cerebral NS; and 4) the frequent finding of numerous eggs concentrated in one area of the spinal cord or brain. One can easily appreciate the intensity of the destructive action on the nervous tissue and the mass effect produced by numerous eggs lodged together in a confined area surrounded by granulomas; in the necrotic-exudative stage these may reach up to 100 times the volume of an egg (73) and characterize the tumoral form of NS.

In a reduced number of NS subjects showing neurological manifestations, particularly those who were living in an endemic area at the time of their first exposure, or in uninfected persons who enter an endemic area for the first time, CNS involvement starts also in the early stages of infection, during or immediately after the acute clinical disease (20,67,68,87,97), i.e., the acute toxemic form (*S. mansoni*) or Katayama fever (*S. japonicum*). In these cases, too, the pathogenesis of CNS lesions depends primarily on the presence of parasite eggs, on host immune response, and on the route of CNS invasion by schistosomes. However, unlike those with the inapparent acute form, these subjects also show a humoral-like immune response to adult worm and egg antigens, elevated serum immunoglobulins probably due to polyclonal activation of B lymphocytes, and immunocomplex formation and deposition. While no pathological studies of NSJ cases associated with the Katayama fever are available to allow definite conclusions, the exacerbated humoral response observed in these cases may partly explain the multiple focal lesions revealed by computerized tomographic (CT) scanning of the brain and the neurological manifestations suggestive of multifocal brain involvement (68).

Although clinically less significant, NSM cases associated with the hepatosplenic and cardiopulmonary chronic forms are the most frequently observed. However, over the last few decades there has been a reduction in the frequency of CNS involvement in these two clinical forms of schistosomiasis mansoni (54), from 26% and 61.1% in the period 1947-1979, respectively, to 12.7% and 41.7% in the period 1971-1990, respectively (54,101,106). In patients with the hepatosplenic form and, particularly the cardiopulmonary form, the high frequency of egg deposition in the brain and other ectopic sites is due to a high parasite burden, the intense oviposition resulting from it, and continuous embolization of eggs to the lungs and other organs, through the collateral portal-systemic circulation that is formed as a consequence of portal hypertension. The marked reduction in the occurrence of brain involvement in these more severe clinical forms can only be explained by the earlier diagnosis of the parasitosis and by the more efficacious action of the specific chemotherapy now being used (oxamniquine and praziquantel). Both drugs kill the adult worm (60,82), thus preventing oviposition and the consequent embolization of eggs in the circulation. In these clinical forms of the disease, the embolization of eggs from the portal mesenteric system to the brain and, less frequently, to the spinal cord via the arterial system or through retrograde venous flow is thought to constitute the main route of CNS invasion by *S. mansoni* (103). Supporting this claim is the observation that, in most cases, *S. mansoni* eggs are sparsely and randomly distributed in the more highly vascular cerebral structures, i.e. the leptomeninges, cerebral cortex, basal ganglia, pons, cerebellum, choroid plexus, and spinal cord (4,10,49,101,106,110). Although less common, the anomalous migration of adult worms to sites close to the CNS followed by in-situ egg deposition may also explain how some patients with the hepatosplenic and cardiopulmonary forms develop NSM. The observation of adult worms in cerebral leptomeningeal veins (10) and of numerous eggs lodged within one area of the brain (4,101) appear to validate this claim. Unlike what is observed when the other clinical forms mentioned above are present, destructive action on the nervous tissue and a mass effect from the parasite-host interaction are not likely to occur in NSM patients with the hepatosplenic and cardiopulmonary forms. This is due to the sparse distribution of eggs and the less intense periovular inflammatory reaction that are associated with these chronic forms of the disease (103).

The cases of NSH associated with obstructive uropathy (severe urinary schistosomiasis) are equally frequent (28% to 56% of patients with this clinical form) and similarly of little or no clinical significance (5,49,50). In these cases, embolization of eggs from the portal mesenteric-pelvic system to the spinal cord and brain through retrograde venous flow probably constitutes the principal route of CNS invasion by *S. haematobium*. The smaller clinical significance of these NSH cases, as in *S. mansoni* cases, is attributable to the sparse distribution of eggs and to the scant periovular inflammatory reaction observed in the chronic forms of the schistosomal infection.

Pathology

As in other organs affected by schistosomal infec-

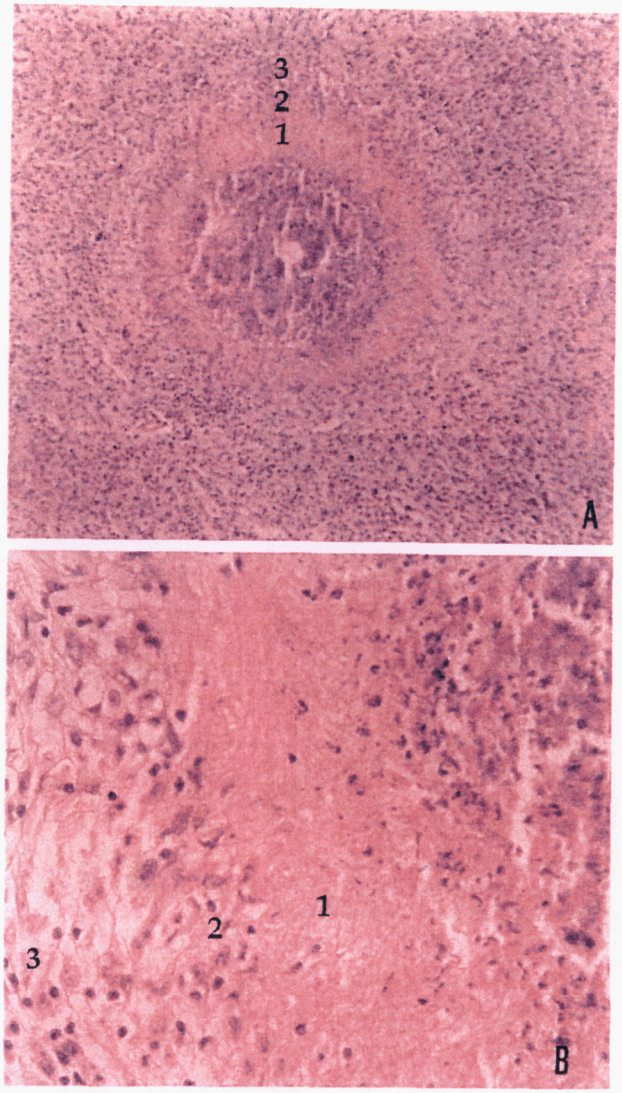

Figure 1. NSM. **(A)** and **(B)**. Necrotic-exudative granulomas, with a central zone of periovular necrosis (1), epithelioid cells lying radially to the zone of necrosis (2), and mononuclear cells (3). H&E, **(A)** X113, **(B)** X450.

tion, the periovular granulomatous reaction in the CNS comprises three stages (73): a necrotic-exudative stage, a productive stage, and a healing by fibrosis stage. In the necrotic-exudative stage, the granuloma is large, with one or more embryonated eggs lying in its center. A zone of necrosis consisting of an eosinophilic, hyaline, homogeneous, PAS-positive substance, in some cases permeated by cellular debris, characterizing the Splendore-Hoeppli phenomenon, is frequently noted around the egg. Immunocomplexes formed by soluble egg antigens, IgM, C3 and the major basic protein granule from eosinophils are commonly found in this zone. Numerous polymorphonuclear cells, mainly eosinophil granulocytes, and, more externally, lymphocytes, plasmacytes and macrophages, may be observed around the zone of necrosis or, this zone being absent, around the egg (Fig. 1 A and B). Not rarely, the macrophages are identifiable as elongated

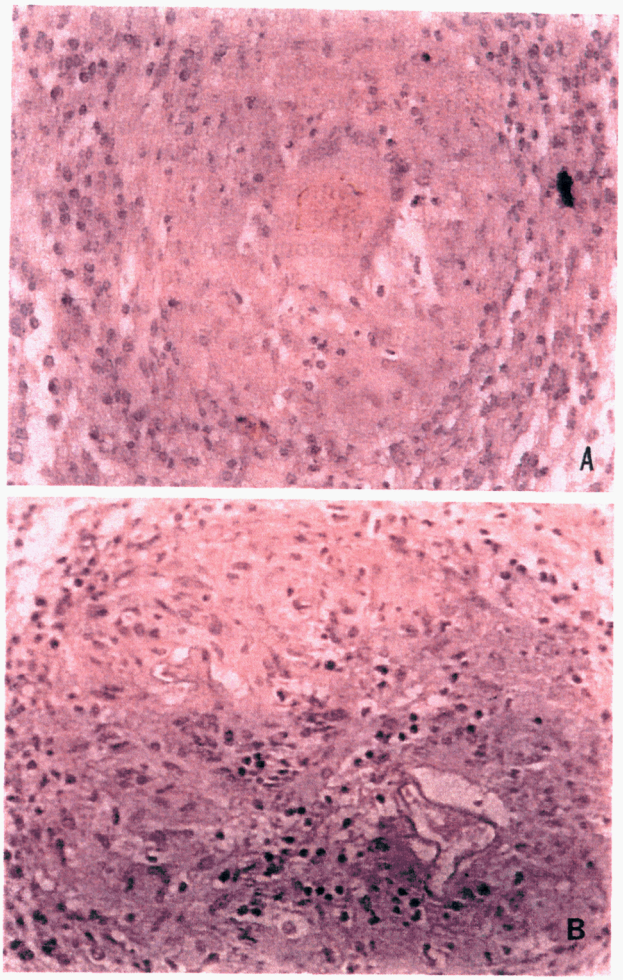

Figure 2. NSM. Productive-stage granulomas, with epithelioid and multinuclear giant cells around egg **(A)** and egg shells **(B)**. **(A)** and **(B)**, H&E, X450.

epithelioid cells lying radially to the center of the granuloma. The nervous tissue adjacent to the granulomas shows congestion, edema, vascular proliferation, endothelial tumefaction, astrocytic reaction and, less frequently, demyelination foci. Necrotic-exudative granulomas are characteristic of the early (acute) stages of schistosomiasis, and may be found within 70 to 110 days following infection.

Productive-stage granulomas are usually smaller than necrotic-exudative ones. The eggs are rarely embryonated; they are often partially empty and, in some cases, only a fragmented, deformed shell is found. The zone of periovular necrosis is no longer present and the inflammatory reaction around the egg consists of a variable number of epithelioid and multinuclear giant cells of the foreign-body type, rarely of the Langhans type, surrounded by lymphocytes and plasmacytes (Fig. 2). Scarce astrocytic reaction is noted around the granuloma.

Granulomas in the healing by fibrosis stage are usually smaller than those in the productive stage. Fragments of the egg shell, surrounded by isolated multinuclear giant cells and a few epithelioid cells

and lymphocytes, may be observed in the center of the granuloma. Around these inflammatory cells is a zone of fibrosis; the older this zone is, the less fibroblasts it contains and the more hyalinized it is (Fig. 3). This appears to be the final stage of evolution of necrotic-exudative granulomas formed during the early (acute) stages of infection (17). However, in patients with the chronic forms of schistosomiasis (hepatosplenic and cardiopulmonary forms, and severe urinary schistosomiasis), an area of discrete fibrillary astrocytosis replacing the zone of fibrosis is usually identified in granulomas in the healing by fibrosis stage (101).

In addition to the periovular granulomatous reaction, eggs surrounded by mononuclear inflammatory infiltrate of variable intensity may also be noted. Other areas may show eggs with no inflammatory reaction (Fig. 4) or with only a zone of discrete fibrillary astrocytosis around them (101,106). The latter are found almost exclusively in patients with the chronic forms of schistosomiasis mansomi (hepatosplenic and cardiopulmonary forms) or with severe urinary schistosomiasis.

Perivascular inflammatory infiltration and vascular cerebral lesions are commonly present in patients with NSM. Proliferative endarteritis and venous thrombosis have been reported in rare instances of symptomatic NSM associated with slight visceral involvement (intestinal and hepatointestinal forms). Fibrinoid-type necrotizing arteritis affecting small-caliber cerebral arteries is observed in about 25% of hepatosplenic patients with NSM (101). These necrotizing vascular lesions appear to be produced directly by schistosomal eggs and granulomas, although they may also be caused, in addition to the presence of eggs in the lumen of cerebral arteries, by the deposition of immunocomplexes in the arterial wall. Immunoglobulins and complement system fractions are commonly found in the choroid plexus of patients with hepatosplenic schistosomiasis (104). The importance of these vascular lesions lies in the fact that they may represent a rare cause of fatal cerebral and cerebellar hemorrhage in patients with the hepatosplenic and cardiopulmonary forms (83,108, 112). Other cerebral arterial lesions observed, generally associated with necrotizing arteritis, are probably sequelae of arteritis or of the passage of eggs through the vascular wall; they are characterized by focal segmental interruption of the internal elastica limitans, sometimes accompanied by thinning of the arterial wall (101).

Macroscopic changes are present in NS only when there is destructive action on the nervous tissue and a mass effect produced by numerous eggs and granulomas concentrated in one area. In other words, they are found only in symptomatic NS patients with slight visceral involvement (intestinal and hepatointestinal forms, and mild urinary schistosomiasis).

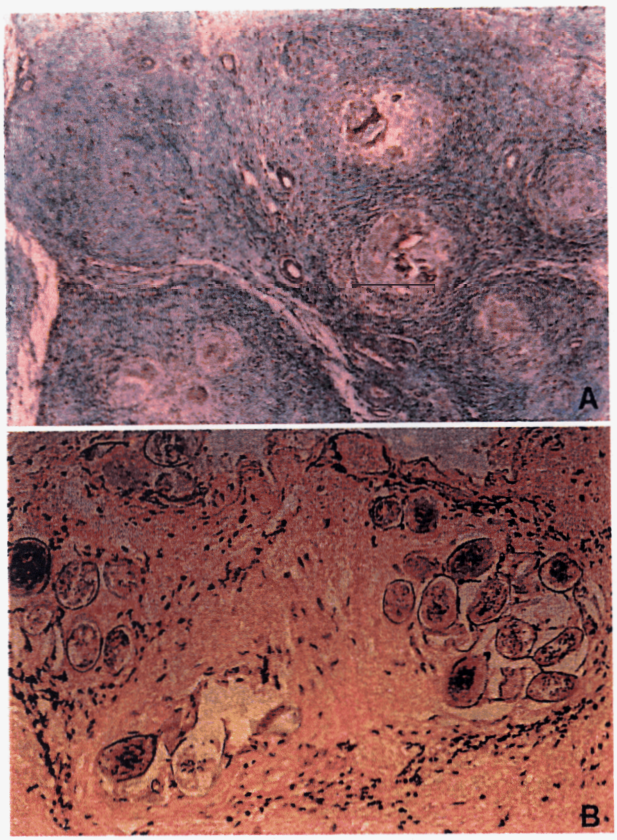

Figure 3. NSM **(A)** and NSJ **(B)**. Granulomas in the healing by fibrosis stage. **(A)** Gomori's trichrome, X113. **(B)** H&E, X256. **(B)** is a courtesy of Dr. G. Watt

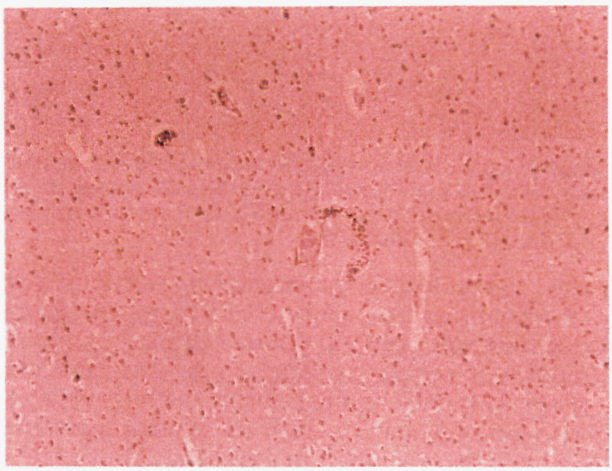

Figure 4. NSM in a patient with the hepatosplenic form. Cerebral cortex. Egg with no inflammatory reaction. H&E, X113.

In addition to a yellow-white, gray-white or slightly brown tumoral lesion of firm consistency and usually well-defined though irregular borders, partial softening of the affected area and small nodules on the cortex and in the subcortical white matter have also been described in patients with the tumoral form of cerebral NSM. The most common site of the lesion is the cerebellum, followed by the

occipital and frontal lobes. In one patient the lesion was attached to the internal face of the dura mater, mimicking a meningioma (105).

The tumoral form of cerebral NSH is very rare. The macroscopic description of the brain lesions is poor in the only surgically treated patient (27,56,107). The lesion was adhering to the falx in the occipitoparietal region. A nodule of firm consistency, measuring 5.0 cm in diameter, located in the choroid plexus of the left lateral ventricle was a surprise finding at autopsy in another patient who died of lung cancer (28). Microscopic examination of the lesion showed numerous eggs, some of which calcified, and adult *S. haematobium*.

The tumoral form of cerebral NSJ is macroscopically characterized by the presence of a conglomerate of nodules varying in size from a few millimeters to 2-3 cm, not encapsulated, though with well-defined limits, of firmer consistency than the surrounding nervous tissue. The lesion has a yellow-white or yellow-gray color, and small yellow foci of necrosis are usually noted. Adhesions between the dura or the pia mater and the arachnoid membrane, in correspondence with the affected cerebral area, are commonly identified. Any cerebral area may be the site of tumoral NSJ lesions, yet the parietal and occipital lobes either in isolation or in association, are involved in 50% of the cases (67,125).

As for the cases of cerebral NSJ associated with the Katayama fever, no pathological studies, as mentioned before, are available to allow to establish an anatomical basis for the clinical and CT abnormalities observed.

In the spinal cord of cases of NSM and NSH, the most frequent changes are congestion of the leptomeninges and swelling of the conus medullaris. The latter has a yellow-white or gray-white color, and shows edema, softening and poor delimitation between white and gray matter. Though less frequent, involvement of the nerve roots of the cauda equina may also occur. In a few cases, small 1-2 mm whitish nodules are noted on the pia mater, within the spinal cord and on the nerve roots. In most of the patients with spinal cord NS, eggs and granulomas are found in the lumbosacral segments of the spinal cord (conus medullaris), sometimes (in *S. mansoni* infection) also in the inferior thoracic and, more rarely, cervical segments. In a few NSM cases, the thoracic segments are predominantly or exclusively involved (102). Massive necrosis of the spinal cord, affecting the lower two thirds of the thoracic segment and the entire length of the lumbosacral segment, interpreted as secondary to a humoral-type hypersensitivity reaction, has been reported in one case of NSM (111). When symptoms have been present for several years, the spinal cord may be macroscopically normal, or it may show atrophy and reduced consistency, these being limited to the more heavily affected cord segment. In these cases, partial

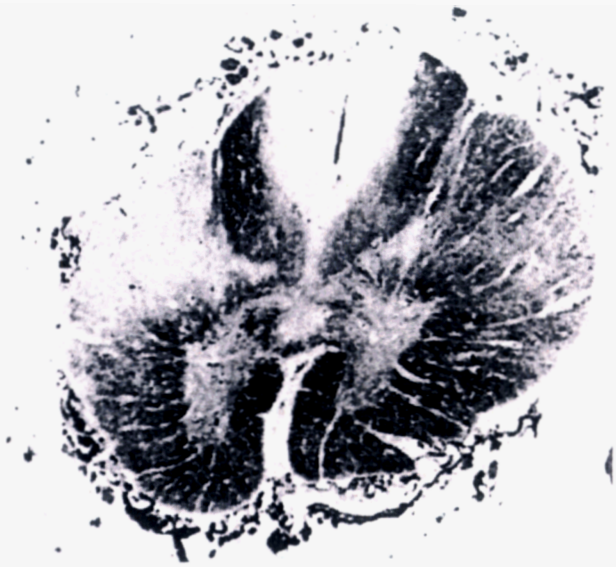

Figure 5. Sequelae of spinal cord NSM. Loss of the nerve fibers of the medial portion of the posterior columns, bilaterally, and of the spinocerebellar tracts and lateral corticospinal tract, unilaterally. Weil-Weigert, X5.7. Reproduced with permission from reference 102.

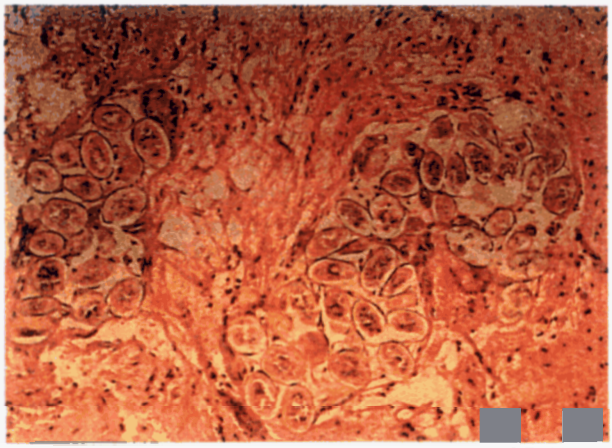

Figure 6. NSJ. Cluster of eggs in nerve tissue. H&E, X256. Courtesy of Dr. G. Watt.

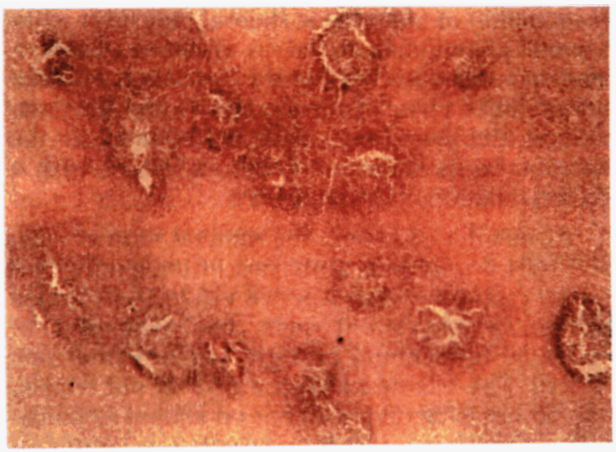

Figure 7. NSM. Numerous necrotic-exudative granulomas. H&E, X45.

atrophy of the lateral and posterior columns, probably secondary to the prolonged destructive action of the granulomas on the nerve fibers, leading to Wallerian degeneration of the affected tracts (Fig. 5), may be found (102).

Clinical Aspects

As mentioned before, neurological symptoms may occur in NS whenever there is destructive action on the nervous tissue and a mass effect produced by numerous eggs and granulomas concentrated in one area (Figs. 6 and 7). As previously discussed in the pathogenesis of NS, involvement of the CNS by *Schistosoma* begins, in the majority of cases, in the early stages of the infection, while the patient is still asymptomatic (inapparent acute form), or during the slow and gradual evolution of the disease to its chronic forms, or still, concomitantly with the chronic intestinal, hepatointestinal and mild urinary forms. As a result, the medical history of patients with clinically symptomatic NS shows that (103); 1) non-neurological symptoms precede the neurological alterations; and 2) the physical examination of the thoracic and abdominal organs of these patients reveals no abnormalities such as hepatosplenomegaly or portal and pulmonary hypertension. Thus, only alterations related to the CNS are evidenced by the medical history and clinical examination of symptomatic NS patients. Cerebral and spinal cord NS will be considered separately here.

Cerebral NS. Only 12 histologically confirmed cases of the tumoral form of cerebral NSM have been reported since 1984 (6,9,15,17,52,53,71,105,118). Of these, 9 were male and 3 female. The patients' ages ranged from 11 to 40 years. The clinical manifestations described were due to an increase in intracranial pressure and focal signs caused by the mass effect produced by numerous granulomas grouped in confined areas of the brain. Duration of the symptoms varied from one week to one year and four months. In most of the cases, the symptoms lasted 3 months or less. In all 12 patients, histopathological examination of brain tissue showed numerous schistosomal granulomas in various evolutive phases. A tendency was observed toward correlation between the evolutive phase of the granuloma and the duration of the symptoms, with granulomas in the necrotic-exudative phase being associated with a shorter duration of the symptoms.

As mentioned before, the tumoral form of cerebral NSH is very rare. Only two histologically confirmed cases have been reported (27,28,56,107). One patient, a 30-year-old male, had symptoms of increased intracranial pressure and was surgically treated. The second patient, a 59-year-old female, had no neurological alterations on clinical examination. Autopsy revealed a nodular lesion located in the choroid plexus of the left lateral ventricle containing numerous eggs and adult worms (28).

From 1889 to 1970, 62 histologically confirmed cases of the tumoral form of cerebral NSJ were reported (7,23,57,67,113,125,132). About two dozen other cases were described in the past two decades. In endemic areas of China, CNS involvement by *S. japonicum* is estimated to occur in 1.7-4.3% of adult hospital patients with schistosomiasis (79). The neurological manifestations of cerebral NSJ may vary, depending on whether CNS involvement occurs 1) during or immediately after the acute symptomatic form (Katayama fever); or 2) after the inapparent acute form.

CNS involvement during or immediately after the Katayama fever occurs occasionally (about 2% of the cases). The patients are invariably young adult males. The neurological manifestations first become apparent after a short period (3 weeks in average) of non-neurological symptomatology, which includes fever, malaise, anorexia, coughing, urticaria, diarrhea, and abdominal pains. A variety of neurological symptoms is observed, including headache, vomiting, speech disturbances, disorientation, visual abnormalities, urinary incontinence, ataxia, motor deficit, usually represented by hemiplegia, hemiparesis or quadriplegia, and coma. Some of these clinical alterations are transient and disappear within a few days or weeks.

The tumoral form of cerebral NSJ occurs more frequently in patients who had the inapparent acute form of schistosomiasis. About 90% of the cases are male. Adults, especially between 20 and 40 years of age, are usually affected. Generalized or jacksonian seizures accompanied by loss of consciousness are the most frequently observed neurological symptoms. Headache, visual abnormalities, and sensory disturbances preceding or not the seizures, papilledema, hemiparesis, and dysphasia are also commonly observed. The clinical signs and symptoms vary according to the site of the cerebral lesions. In some cases, the neurological examination may show no abnormalities. Duration of the symptoms varies from 3 weeks to one year.

Spinal cord NS. Over the period between 1930, when the first case of spinal cord NSM was reported, and 1995, 65 cases of histologically confirmed spinal cord NSM were described (1,2,8,16,19,20,22,24, 30-34,36,38,40,43-49,51,55,63,66,69,70,72,77,78, 80,81,84-86,88,89,91,93,94,97,101-103,109-111,114-117,119-121,126,129). From 1936 to 1994, reports of 21 histologically confirmed cases of NSH were published (3,12,13,35,38,39,49,50,56,59,66,90, 96). More than 80% of the patients were male. While all age groups may be affected, most of the patients were young adults, teenagers and children. Similarly to those of cerebral NS, the clinical symptoms of spinal cord NS are secondary to the site of location of schistosomal eggs and granulomas and to the mass effect produced by the latter.

In the majority of the cases, duration of the symptoms varies from a few days to six months; in

about half of these, they last less than one month. The remainder cases show symptoms persisting from seven months to six years. An initial burning pain radiating from the thoracolumbar region of the back toward the lower limbs, followed by flaccid paraplegia, sphincter dysfunction, hypo- or areflexia, and sensory disturbances from the pelvic girdle down, is the characteristic presentation. The pain usually subsides with the onset of paraplegia. In more than half of the cases, the time between appearance of the initial symptoms and the onset of paraplegia varies from less than 24 hours to a few days or one week. When higher segments of the spinal cord are involved, spasticity is usually present. Atrophy of the skeletal muscles of the lower limbs is observed in rare instances of spinal cord NS, and it is not necessarily associated with a lengthier progression of the symptoms.

As discussed in the pathogenesis section, neurological symptoms attributable to egg deposition are not usually observed in NSM patients with the hepatosplenic and cardiopulmonary forms or in NSH patients with severe urinary disease. The marked clinical alterations noted in these patients result from; 1) the portal hypertension and pulmonary hypertension syndrome (hepatosplenomegaly, ascites, collateral cutaneous circulation, high digestive hemorrhage from ruptured esophageal varices, cardiomegaly, chronic cor pulmonale, right heart failure, etc.); and 2) severe urinary schistosomiasis and related complications (hydrourether, hydronephrosis, pyelonephritis, renal failure, bladder cancer). However, seizures may be produced by the sparsely distributed eggs and even by the less intense periovular inflammatory response that are observed in these cases. The frequency of seizures was 10% in 29 autopsied patients that had cerebral and hepatosplenic schistosomiasis mansoni, whose medical history was known (103). Although rarer, another possibility for the appearance of neurological symptoms in patients with cerebral, hepatosplenic and cardiopulmonary schistosomiasis mansoni is through the occurrence of fatal cerebral and cerebellar hemorrhage. Only 3 such cases, two of which with cerebral and one with cerebellar hemorrhage, have been described (83,108,112). Symptoms of increased intracranial pressure were present in all three cases. Focal signs were present in one of the patients. Duration of the symptoms was 2, 11 and 23 days.

Other clinical alterations and neuropathological changes not directly related to *Schistosoma* may be found in patients with the hepatosplenic form of schistosomiasis mansoni and japonica. They are attributable to portal hypertension and to the consequences resulting from it, i.e., hepatic encephalopathy, of relatively rare occurrence, and type II Alzheimer astrocytoses, similar to that observed in liver cirrhosis (99,100).

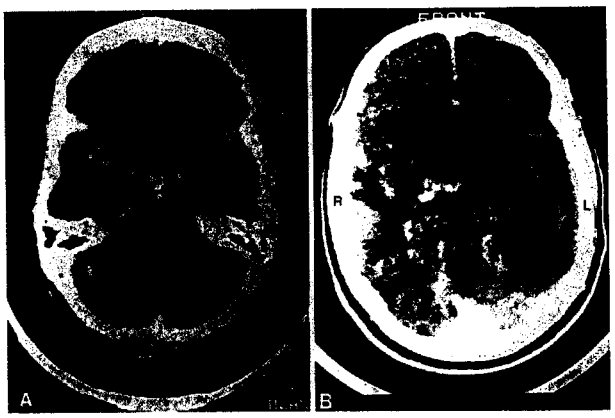

Figure 8. Cerebral NSM. CT scan shows a hyperdense enhancing area in the cerebellar vermis **(A)** and in basal ganglia and thalamus **(B)**. In **(B)** there is a hypodense halo surrounding the hyperdense area. **(A)** is a courtesy of Dr. G. Cabral.

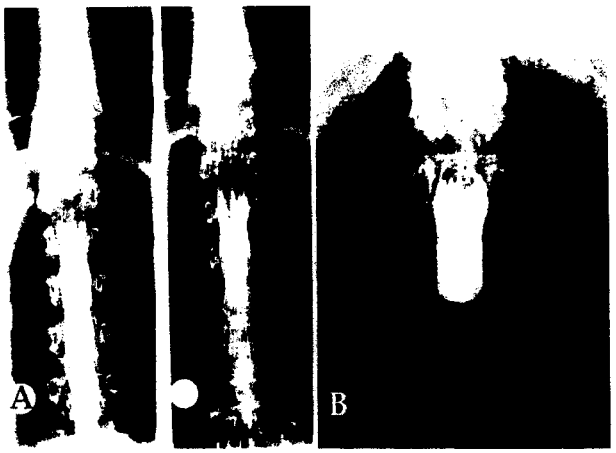

Figure 9. Spinal cord NSM. **(A)** and **(B)**. Myelography shows irregular trifid edges, at the T12-L1 level. Courtesy of Dr. A.V. Giannetti **(A)** and Dr. G.B. Campos **(B)**.

Diagnosis

The clinical features of the tumoral form of cerebral NS are usually not distinguishable from those of any other slow-expanding intracranial lesion, since no neurological symptoms or CT findings are specific for cerebral NS. Except for neurological alterations, no other abnormalities are noted on physical examination. Laboratory examinations are of little help in establishing the etiological diagnosis of the expansive lesion, as either they are performed after surgery or they reveal intestinal infection only. Eosinophils are often identified in the blood. The presence of eggs in the feces or in rectal snips (*S. mansoni* and *S. japonicum*) and in the urinary sediment (*S. haematobium*) is a frequent finding. CT scan shows a hyperdense, enhancing area surrounded by a hypodense halo (Fig. 8), with an associated mass effect (105). In some cases, an initial CT scan may reveal no abnormalities. A magnetic resonance imaging (MRI) scan was obtained in a patient and showed a homogeneous contrast-enhancing lesion with surrounding edema (27,56,107). In all reported cases of tumoral

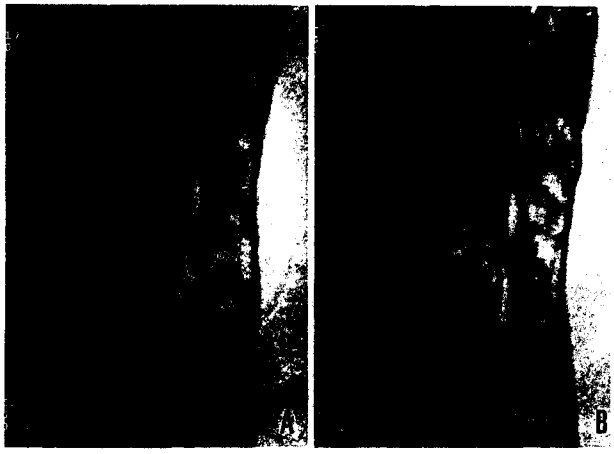

Figure 10. Spinal cord NSM. MRI scan (T1 weighted) of the thoracolumbar region before **(A)** and after **(B)** gadolinium injection. There is enlargement of the conus medullaris with spotty enhancement after contrast injection. Courtesy of Dr. A.V. Giannetti.

NS, the diagnosis was established with basis on the identification of eggs and granulomas in nervous tissue removed surgically or at autopsy.

The clinical diagnosis of spinal cord NS, on the other hand, may be strongly suggested when a patient from an endemic area presents with rapidly progressing signs and symptoms of transverse myelitis involving the lumbosacral segments of the spinal cord (conus medullaris). The clinical diagnosis becomes less clear when the higher segments of the spinal cord are involved or when there is a slower progression of the neurological signs and symptoms. Except for the presence of neurological alterations, the physical examination reveals no other abnormalities. Eosinophils are frequently found in the blood. In most of the cases, the cerebrospinal fluid is clear and shows mild pleocytosis, with lymphocytes predominating; protein levels are usually raised; glucose levels are normal (120). Eosinophils are not often found in the cerebrospinal fluid. In about 60% of the cases, *S. mansoni* eggs are identified in the feces. When the feces examination is repeatedly negative, rectal biopsy is resorted to, for its greater positivity. Especially in cases showing a more chronic evolution, parasite eggs may not be obtained from feces or rectal snips. In 25% of the cases, *S. haematobium* eggs are identified in the urine and sometimes in the feces or in rectal snips.

Many immunological tests, including intradermal reaction, indirect hemagglutination, complement fixation, circumoval precipitin, flocculation, and indirect immunofluorescence tests, as well as the enzyme-linked immunosorbent assay (ELISA), have been used to assess reactivity to *S. mansoni, S. haematobium* and *S. japonicum* antigens in patients with clinical evidence of NS (120). Many of these tests have high sensitivity but limited specificity, and besides, a positive reaction is only evidence of exposure to *Schistosoma*. The role of serological tests on cerebrospinal fluid in the diagnosis of NS has not been fully elucidated. In the last few years, the determination of concentrations of anti-soluble egg antigens IgG detected by the ELISA test in the cerebrospinal fluid has been recommended for the diagnosis of spinal cord NS (42,59,92). Tests involving the use of monoclonal antibodies directed against purified antigens from these three schistosomal species, although likely to become important in the future, still lack large-scale application.

Myelography in spinal cord NSM and NSH patients (Fig. 9) usually reveals a partial or complete block extending the length of a vertebral body, with irregular trifid edges and an abrupt swelling of the affected cord segment, at the T12 to L1 level (38). A normal myelogram may be obtained in recently infected or less seriously affected patients. CT scan shows fusiform swelling of the conus medullaris (59,66). A decrease in conus size may be observed in a few weeks and months after treatment with praziquantel and corticosteroids (59). MRI (Fig. 10) reveals an enlarged spinal cord (usually of the conus medullaris) with spotty enhancement after gadolinium injection (21,37,80,126). Spinal cord atrophy may be demonstrated on CT and MRI some months after the initial clinical presentation (59,126).

Laminectomy and spinal cord biopsy to demonstrate the presence of schistosomal eggs and granulomas, though increasingly less used now, remain the only procedures by which a safe diagnosis of spinal cord NS can be established. These procedures, however, carry an unacceptable risk in the cases in which there is no radiographic evidence of spinal cord compression (21).

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