Involvement of Central Nervous System in the Schistosomiasis

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The involvement of the central nervous system (CNS) by schistosomes may or may not determine clinical manifestations. When symptomatic, neuroschistosomiasis (NS) is one of the most severe presentations of schistosomal infection. Considering the symptomatic form, cerebral involvement is almost always due to Schistosoma japonicum *and the spinal cord disease, caused by* S. mansoni *or* S. haematobium. *Available evidence suggests that NS depends basically on the presence of parasite eggs in the nervous tissue and on the host immune response. The patients with cerebral NS usually have the clinical manifestations of increased intracranial pressure associated with focal neurological signs; and those with schistosomal myeloradiculopathy (SMR) present rapidly progressing symptoms of myelitis involving the lower cord, usually in association with the involvement of the cauda esquina roots. The diagnosis of cerebral NS is established by biopsy of the nervous tissue and SMR is usually diagnosed according to a clinical criterion. Antischistosomal drugs, corticosteroids and surgery are the resourses available for treating NS. The outcome is variable and is better in cerebral disease.*

Key words: schistosomiasis - neuroschistosomiasis - central nervous system/parasitology - *Schistosoma mansoni* - *Schistosama japonicum* - *Schistosoma haematobium*

ETIOLOGY AND EPIDEMIOLOGY

The term neuroschistosomiasis (NS) refers to the symptomatic or asymptomatic involvements of the central nervous system (CNS) by schistosomes. When associated with clinical symptoms, it is one of the most severe presentations of schistosomal infection. NS can be caused by *Schistosama japonicum*, *S. mansoni*, and *S. haematobium*. Considering the symptomatic form, the last two species are almost always associated with a myeloradicular syndrome and the first species, with cerebral disease.

Symptomatic cerebral NS has been recorded in about 2-4% of individuals infected with *S. japonicum* (Watt et al. 1986). On the other hand, this form of presentation is very rare in association with the other two species. Schistosomal myeloradiculopathy (SMR) is less frequent than cerebral disease. There are around 500 cases reported since the description of the entity in 1930. Although SMR is considered a rare form of NS, its prevalence is unknown and some authors believe that this entity has been underdiagnosed (Joubert et al. 1990, Haribhai et al. 1991, Ferrari 1997, Silva et al. 2003). This possibility is reinforced by the greater number of cases published as knowledge of the disease spreads and by the relatively large number of patients seen by some investigators during a short time (Asano 1992, Ferrari 1997, Peregrino et al. 2002). *S. mansoni* is the species responsible for the great majority of the reported cases of SMR (Ferrari 1999).

As demonstrated by necropsy studies (Scrimgeour & Gajdusek 1985, Gonçalves et al. 1995), asymptomatic deposition of schistosomal eggs in the more highly vascular cerebral structures is more frequent than the symptomatic forms of NS.

PATHOGENESIS

Several aspects of the pathogenesis of NS are unknown, although available evidence suggests that the lesions seen in the CNS depend basically on the presence of parasite eggs in the nervous tissue and on the host immune response. The eggs can reach the CNS at any time of the infection; however, in the great majority of the cases associated with neurological symptoms, the involvement of the CNS occurs during the evolution of the infection to its chronic phase or concomitantly with the less severe chronic forms (i. e., intestinal and hepatointestinal forms – for *S. mansoni* and *S. japonicum*, and urinary forms without obstructive uropathy – for *S. haematobium*). On the other hand, asymptomatic NS is much more common in association with the more severe chronic forms of *S. mansoni* and *S. haematobuim* infection (i. e., hepatosplenic and cardiopulmonary forms for the first species and obstructive uropathy for the latter) (Pittella 1991, 1997, Ferrari 1999).

It is believed that in symptomatic NS the eggs reach the CNS through retrograde venous flow into the Batson vertebral epidural venous plexus, which connects the portal venous system and venae cavae to the spinal cord and cerebral veins. This route permits either anomalous migration of the adult worms to sites close to the CNS followed by in situ oviposition, or massive embolization of eggs from the portal mesenteric-pelvic system. The small round eggs of *S. japonicum* travel all this way and reach the brain; on the other hand, *S. mansoni* and *S. haematobuim* eggs, which are larger and bear protruding spines, are retained in the lower spinal cord. Once deposited in the nervous tissue, the mature embryo secretes and excretes antigenic and immunogenic substances that account for the periovular granulomatous reaction. A large

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number of eggs and granulomas lodged together in circumscribed areas of the CNS cause damage to the adjacent nervous tissue by the inflammatory reaction itself and by the mass effect (Scrimgeour & Gajdusek 1985, Pittella 1991, 1997, Ferrari 1999).

According to Pittella (1991, 1997), in the asymptomatic form of NS, the eggs can reach the CNS either by the route described above (which is favored by the portal hypertension that, apparently, causes these anastomoses to open up more easily), or via the arterial system. The eggs may pass into the arterial circulation through previously developed pulmonary arteriovenous shunts or through portopulmonary anastomoses via the azygos vein, which form as a consequence of the portal hypertension. The lack of symptoms is attributed to the sparse distribution of the eggs and to the scant periovular inflammatory reaction observed in these severe chronic forms of the schistosomal infection.

CLINICAL MANIFESTATIONS

Patients with NS usually present only the symptoms due to the CNS involvement. Symptomatic NS is very rare either during the acute phase of the infection or in association with the severe chronic clinical forms (Pittella 1997, Ferrari et al. 2001). All the forms of symptomatic NS are more prevalent among young men.

It is important to comment here on a different form of symptomatic NS, not mentioned before in this text. It develops in a few patients, mainly at the time of the first exposure to schistosomes, and is more frequent with *S. japonicum* infection. The disease usually presents as an acute encephalitis or encephalomyelitis together with or immediately after the systemic manifestations of the acute phase, which include fever, headache, malaise, anorexia, coughing, skin rash, diarrhea and abdominal pain (Case Records 1996). These clinical manifestations (systemic and neurological), as a rule, are transient lasting a few days or weeks, and treatment is usually followed by complete recovery (Blankfein & Chirico 1965). This picture has been attributed to a humoral-like immune response to adult worm and egg antigens with elevation of the serum immunoglobulins and immunocomplex formation and deposition (Pittella 1997).

Cerebral NS often presents as a slow-expanding intracranial lesion. The clinical manifestations are variable and depend mainly on the site of the lesion and on the increase in the intracranial pressure caused by the mass effect of the granulomas. Headache, seizures, papilledema, visual abnormalities, speech disturbances, sensory impairment, hemiparesis, nystagmus, and ataxia are common manifestations. Duration of the symptoms varies from a few weeks to more than one year (Pittella et al. 1996).

Although also nonspecific, the clinical picture of SMR is usually suggestive when observed in a patient with epidemiological antecedents for schistosomal infection. The disease more frequently starts with lumbar pain and/or pain in the lower limbs, usually of a radicular nature, which is followed, often within hours to a few days, by muscular weakness and sensory impairment in the lower limbs, almost always associated with autonomic dysfunction, particularly bladder dysfunction. The localization in the lower spinal cord and/or cauda equina, the rapid progression of the neurological picture, and the association of symptoms due to spinal cord and nerve roots involvement are the most characteristic clinical elements of SMR (Ferrari 1999). Although the neurological manifestations of the entity are quite constant, their intensities vary a lot among the patients and the disease tends to progress with higher and more significant spinal cord involvement (Ferrari 1997, 1999). It is important to point out that the clinical picture of SMR may be occasionally less suggestive of the entity. It occurs mainly when higher segments of the spinal cord are involved or when there is a slower progression of the neurological signs and symptoms.

DIAGNOSIS

The clinical features of cerebral NS are usually not distinguishable from those of any other slow-expanding intracranial lesion, as no neurological symptoms or imaging findings are specific for the entity. Thus, histopathological examination of the nervous tissue is the only definitive means of establishing the diagnosis. On the other hand, the clinical diagnosis of SMR may be strongly suggested when a patient from an endemic area presents with rapidly progressing signs and symptoms of myelitis involving the lower spinal cord segments, usually in association with involvement of the cauda esquina roots. Therefore, the diagnosis of SMR is usually established according to the following criterion: evidence of a medullary lesion (low thoracic, lumbar and/or sacral medulla) and/or lesion of the cauda equina; confirmation of schistosomal infection by a direct method (stool parasitological examination and/or rectal biopsy for *S. mansoni*); and exclusion of other causes of the myeloradicular damage (Ferrari et al. 1993).

The chemical and cytomorphologic examination of the cerebrospinal fluid (CSF) usually show an inflammatory pattern characterized by increase in the total protein concentration and pleocytosis mainly involving lymphocytes. Eosinophils may or may not be present. Although the finding of eosinophils in the CSF can contribute to the diagnosis of NS (especially SMR), it is also nonspecific since this cell type can be seen in several other conditions (Case Record 1996).

In symptomatic cerebral NS, computerized tomography (CT) usually shows a hyperdense, enhancing area surrounded by a hypodense halo due to edema, with an associated mass effect. Multiple focal lesions may be seen. Magnetic resonance imaging (MRI) demonstrates one or more areas of hypointense and hyperinthese signals with contrast enhancement. Myelography, CT-myelography, and MRI of the spine also show unspecific findings. The most frequent abnormalities are enlargement of the spinal cord, more frequently the conus medullaris, associated or not with thickening of the cauda equina roots. Sometimes MRI shows areas of hipo/hiperintense signals with contrast enhancement without any changes in the diameter of the spinal cord.

The search for antibodies against shistosomal antigens in the CSF has been considered useful for the diagnosis of symptomatic NS. Serological methods have been better studied in SMR (Pammenter et al. 1991, Ferrari et al.

1995, 1999); however, their role has not been completely defined.

TREATMENT AND OUTCOME

Antischistosomal drugs, corticosteroids, and surgery are the modalities of therapy available for treating NS. Antischistosomal drugs cause death of the adult worm, resulting in cessation of oviposition and thus a reduction in the inflammatory response. Corticosteroids are expected to diminish granulomatous inflammation and edema, thereby reducing the compression and destruction of the nervous tissue. In addition, there is some evidence that such drugs reduce egg deposition by the adult worms (Fowler et al. 1999). Surgical approach should be individualized.

At present, a consensus has not been reached on the optimal mode of therapy for all presentations of cerebral schistosomiasis. According to the review by Fowler et al. (1999), in a patient with neurological symptoms and cerebral lesions believed to be caused by a schistosomal infection, prompt medical therapy with both praziquantel (PZQ) and a corticosteroid has been shown to be effective. They do not encourage surgical excision unless the diagnosis is uncertain and they believe that minimally symptomatic or asymptomatic patient may be treated with PZQ alone.

We treat SMR with PZQ (60 mg/kg/day for three days) given in two daily doses at a 4 h interval and prednisone (1.5-2.0 mg/kg/day) administered in three daily doses or methylprednisolone 500 mg every 12 h for five days followed by prednisone as described above. This high dose of prednisone is maintained for about 3-4 weeks, followed by progressive reduction over several weeks (Ferrari et al. 1993). Surgical approach, due to the risk of additional damage to the involved nervous tissue, should be reserved for specific cases such as those with evidence of medullary compression, those who deteriorate despite clinical treatment, and when there is considerable diagnosis uncertainty (Scrimgeour & Gajdusek 1985, Ferrari 1999).

Patients treated for NS can present complete, partial or even no recovery. Literature data suggests that outcome is more favorable in the cerebral disease than in SMR. Cerebral NS is associated with a more indolent course and a better response to therapy; on the other hand, residual deficits are more frequent and more severe in the spinal cord disease, which presents a more acute evolution. As the prognosis in SMR depends in part on factors related to the disease itself and in part on early treatment (Ferrari 1999), it has been recommended the empirical use of PZQ in combination with a corticosteroid in suspected cases while the diagnosis has been clarified (Joubert et al. 1990, Haribhai et al. 1991, Case Records 1996). This is especially relevant in the management of patients presenting in rural areas of endemic countries where sophisticated investigative facilities are not usually readily available.

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