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·Minireview·

Research development of the pathogenesis pathways for neuroschistosomiasis

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Abstract: The infection of the central nervous system (CNS) by schistosome may or may not have clinical manifestations. When symptomatic, neuroschistosomiasis (NS) is one of the most severe presentations of schistosome infection. Among the NS symptoms, cerebral invasion is mostly caused by Schistosoma japonicum (S. japonicum), and the spinal cord symptoms are mainly caused by S. mansoni or S. haematobium. There are 2 main pathways by which schistosomes cause NS: egg embolism and worm migration, via either artery or vein system, especially the valveless perivertebral Batson's plexus. The adult worm migrates anomalously through the above pathways to the CNS where they lay eggs. Due to the differences in species of schistosomes and stages of infection, mechanisms vary greatly. The portal hypertension with hepatosplenic schistosomiasis also plays an important role in the pathogenesis. Here the pathways through which NS occurs in the CNS were reviewed.

Keywords: schistosome; neuroschistosomiasis; the central nervous system; pathways; granuloma; pathogenesis

1 Introduction

Schistosomiasis is a neglected tropical disease that ranks with malaria and tuberculosis as a major source of morbidity affecting approximately 210 million people in 76 countries, despite the strenuous control efforts[1,2]. Usually, human can be infected by 3 principal species: Schistosoma japonicum (S. japonicum), S. mansoni and S. haematobium[3]. S. mansoni and S. japonicum are usually found in human portal mesenteric system, inducing digestive symptoms, while S. haematobium often parasitizes in the urinary and the reproductive systems. The neuroschistosomiasis (NS) refers to the involvement of the central nervous system (CNS), symptomatic or asymptomatic. When symptomatic, NS is one of the most severe presentations of schistosomal infection[4]. The pathogenesis of CNS lesions produced by schistosomes depends on both the presence of the parasite eggs in the nervous tissue and the host immune response[5]. Besides, the clinical manifestations including spinal cord symptoms and myeloradiculopathy, are usually caused by S. mansoni and S. haematobium. The eggs of S. japonicum are smaller and can easily reach the brain, causing cerebral NS, incidence of which is about 2%-4%[6]. Here the pathways through which NS occurs are reviewed.

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2 The cerebral NS

There are 2 main mechanisms of cerebral NS: egg embo-

lization (indirect deposition) and adult worm migration (direct deposition)[6-9].

2.1 Egg embolism mechanism Many cases of symptomatic involvement of the encephalon by S. japonicum have been reported, mostly in Chinese literature. S. mansoni and S. haematobium can also induce similar symptoms. However, disorder caused by S. mansoni is not so common as that by S. japonicum, and disorder caused by S. haematobium is even rare[5]. Pittella[8] has reported that the schistosoma adult worms begin laying eggs after mature, and the majority of the eggs deposit in the portal system and the pulmonary system through the arteriovenous anastomosis. Then the eggs enter the pulmonary vein, reaching the brain through the arterial system. Based on the craniotomy and histological analysis of 17 cases of cerebral S. japonicum lesions, Ying *et al.*[9] postulate that the S. japonicum egg deposition transfers probably via the arterial system to the CNS. He explains that the brain lesions are more concentrated in the parietal area, supplied by the middle cerebral artery, and the deposits are mainly located in the local leptomeningeal or the underneath (gray matter and superficial white matter) part, which is consistent with the general rules of embolism. Moreover, among all the 17 cases, there are at least 3 cases in which the eggs clearly exist in the small arteries, which, however, makes it difficuct to interpret the formation of cerebellar focal lesions. Liu *et al.*[10] have reported 33 patients who had been presumptively diagnosed with cerebral schistosomiasis caused by S. japonicum. Brain magnetic resonance imaging (MRI) has shown discrete large lesions with prominent perilesional edema in these patients, composed of characteristic multiple enhancing nodules. Most of these lesions were in the frontal (n=27) lobes, others were in the temporal (n=8), the parietal (n=6), and the occipital (n=4) lobes, distributed in different arteries and veins. However, some authors propose that the cerebral focal lesions and vascular necrosis in autopsy could be interpreted by the vein embolization mechanism. They prefer the cerebral venous egg thrombosis mechanism[8,11,15], although the tumor-like mass granulomas by S. mansoni eggs may be located in any lobe of the brain. According to their reports, the most common site is the cerebellum, which is consistent with the hypothesis that the eggs reach the CNS through retrograde venous flow into the non-valve Batson's venous plexus that connects the portal venous system and venae cavae to the spinal cord and cerebral veins[1,12]. There are abundant vascular mutual shunts in the thoracic and abdominal cavities, either through portopulmonary anastomoses, such as the azygos vein, or through the vertebral venous plexus. Under the conditions of portal hypertension such as coughing and defecation, the intra-abdominal pressure increases, and the venous retrograde blood flow carrys the eggs into the dura sinus via the internal jugular veins[5]. This could better illustrate the formation of cerebellar lesions. Thus, the open-up of vascular mutual shunts are more likely to occur in schistosomiasis patients with portal hypertension.

2.2 The ectopic migration of adult worms This hypothesis maintains the ectopic migration of adult worms to the brain or the spinal cord, where the adult worms lay eggs. The autopsy studies find that S. haematobium and S. mansoni adult worms could invade the leptomeningeal or the pia mater in the subarachnoid space of spinal cord[6,8,13,14]. Besides, S. japonicum adult worms have also been found in the cerebral vein in the experimental monkeys[9,17]. However, S. japonicum worms are seldom found in human brain. Based on the studies of experimental primates with cerebral S. japonicum infection[15], the adult worm invasion of the CNS is discussed. To access the cerebral veins, 3 different stages of development are required: the cercariae stage when they penetrate the skin, the schistosomulae stage when they migrate from lungs, and the final adult worm stage when they migrate from mesenteric veins. Zhang[16] has observed and analyzed 13 cases of cerebral NS by surgical resection. He postulates that the adult worm could enter the intracranial venous sinus (mostly transverse sinus) through ectopic migration, and lay eggs directly in the CNS. He further explains that the lesions are mainly accumulated in the temporal and the frontal lobes, which is different from the general distribution of cerebral artery embolism for parietal and temporal brain lesions. The histopathologic examination on the granulomatous lesions caused by S. japonicum eggs has shown the accumulation of a large number of eggs that are fresh, dead, or calcified in different forms. This finding suggests that the ovulation may

occur in the same site but at different times, since the S. japonicum adult worms produce so many eggs that they could not be disseminated through the same tiny blood vessels. Tang *et al.*[17] have investigated the ectopic migration routes of both S. japonicum adult worm and schistosomula in mice and rabbits with S. japonicum cercariae infection. They find that the number of cercariae is critical for the occurrence of ectopic migration: the larger number of cercariae, the higher chance to reach the CNS. Meanwhile, S. japonicum adult worms and schistosomula are detected in the vertebral veins, and pairing up of adult worms is also observed in the intercostal veins. Zhang[16] proposes that if the egg embolization occurs in the brain, the portal veins or the pulmonary vascular system would have a great burden to clear the eggs, complicated with portal hypertension. Moreover, the development of pulmonary arteriovenous shunts or portopu-lmonary anastomoses, without going by way of heart or lungs, increases the incidence of egg deposition in the CNS. For the lifecycle of the schistosomes, the cercariae penetrate the human skin, and transform to be schistosomula, adapting to the mammalian environment. Then, via the blood vessels and lymphatics, the schistosomula reach the lung. After several days, both male and female worms migrate between the pulmonary and hepatointestinal circulations, and rapidly mature. The adult worms return to the inferior mesenteric veins (S. japonicum) or the superior mesenteric veins (S. mansoni), or reach the veins surrounding the bladder and ureters (S. haematobium) via the portal systemic anastamoses. The female adult worms begin to shed eggs. Totally, it may take 4-6 weeks for migration and maturation, depending on the response of the host and the species involved[8]. As a result of egg-induced chronic presinusoidal inflammation, fibrous material deposition and vascular destruction are induced, which is called "Symmer's pipe-stem fibrosis", indicating a periportal fibrosis without bridging and nodular formation[18]. This would then lead to portal hypertension and cirrhosis, which could increase the possibility of migration to the CNS. Craniotomy and histological analysis are often employed for etiologic diagnosis. However, the development of novel imaging techniques, particularly MRI, facilitates the accurate diagnosis of NS. In Liu's MRI imaging studies, the numbers of the lesions in the frontal and the temporal lobes are 27 and 8, respectively, which provides different imaging aspects for those hypotheses[10]. He has also investigated the cause of linear enhancement on MRI, and postulates that the nodular and linear enhancement may be the result of worm-induced local leptomeningeal vein obstruction and slowing of the blood flow, thus leading to the increase of ova concentration and formation of a nodular mass[19].

3 Spinal cord schistosomiasis and the pathway of vertebral Batson's venous plexus

A great majority of reported cases of spinal cord NS are caused by S. mansoni. However, this can also be caused by S. haematobium, and only a few cases are induced by S. japonicum. Previous reports indicate that these 3 species may cause similar spinal cord disorders[5,8,20-22]. Ferrari *et al.*[5] have discussed the literature data (280 cases) on spinal cord neuroschistosomiasis mansoni (NSM), published from 1930 to 1996. Young adults, teenagers and children of male sex, are more common to be affected, which can be explained by a higher frequency of exposure to fresh water both during childhood and in their work environment[5,20,22]. Actually, concerning the asymptomatic NS, the number of NS patients far exceeds that of the diagnosed cases. Postmortem studies demonstrate that asymptomatic deposition of S. mansoni eggs in the CNS is more frequent than the symptomatic forms of NS by S. mansoni[5,20]. Besides, Pittella[5,8] concludes that the symptomatic S. mansoni-related NS affects far more frequently the spinal cord than the brain. It is believed that S. japonicum eggs have a smooth surface and a smaller and round size ($60\times100\ \mu m^2$), and they can easily access the brain through the blood circulation. Moreover, S. japonicum can shed a great number of eggs (an adult worm typically shed hundreds to thousands of eggs daily). On the other hand, the eggs of S. mansoni ($61\times140\ \mu m^2$) and S. haematobium ($62\times150\ \mu m^2$) usually deposit in the lower part of the spinal cord, due to their larger size and the prominence in their egg shells. The most important clinical feature of S. mansoni infection in spinal cord is the low localization of the lesions. Some researchers conclude that in a great majority of the cases, the medullar level of lesions is T6 or lower, particularly T11-L1, al-

though high levels of T1-T5 or even cervical localization have also been reported in a few cases[5,23,24]. This fact can be attributed to the more frequent anastomoses between the Batson's venous plexus and the portal venous system at this region[5]. In approximately 70% of the cases, it needs 15 d or less to develop from initial manifestation to the full neurological symptoms[5], which is just the lifespan of miracidia in the egg (about 12-15 d). The mature eggs continue to secret and excrete soluble egg antigen (SEA) that elicits the periovular granulomatous reaction. And it takes about 10 d to develop from maturation to death and disintegration[17], which matches the fact that the largest granuloma size is reached by 4-8 d[5]. The early stage of infection is characterized by necrotic-exudative granulomas. Meanwhile, cytokine secretion and immune complex formation reach the maximal levels at this stage. In the subsequent chronic phase, the granulomatous reaction is down-modulated. Granulomas at the productive stage are rarely embryonated, and are usually smaller than necrotic-exudative ones. The granulomas at the fibrosis healing stage are even smaller and induce less inflammatory reactions. During chronic schistosomiasis, the granulomas tend to be relatively small, compared with those formed shortly after the onset of oviposition[8,12].

Based on the clinical presentations, the histopathologic aspects, and findings by imaging methods, Ferrari[5,22] has classified spinal cord schistosomiasis into 4 clinical forms: myelitic (minimal granulomatous response, necrosis and atrophy of the nervous tissue, transverse myelitis, normal myelography, and adverse outcome), granulomatous (intense gliotic and fibrotic reaction around the eggs, enlargement of the spinal cord, and less adverse outcome), radicular (granulomas on the surface of the spinal roots, widening of the nerve roots, multiradicular syndrome, and less adverse outcome), and vascular (rare, vasculitis of the branches of the anterior spinal artery, and less adverse outcome).

In spinal cord schistosomiasis, the eggs may reach the spinal veins via the valveless venous Batson's plexus, either through the retrograde venous flow when the intra-abdominal pressure rises, or after an anomalous migration through leptomeningeal veins of adult S. mansoni worms, as shown by some pathological studies[12]. This happens especially in the patients with advanced hepatosplenic and hepat-ointestinal diseases, known as fibro-obstructive hepatic schistosomiasis, such as liver cirrhosis and portal hypertension. The portal hypertension can play an important role not only in schistosoma egg embolization, but also in worm migration into the CNS.

In Belo Horizonte, Brazil, the postmortem studies[25] on patients during 1949-1979 and 1971-1990 were conducted by Goncalves *et al.* to investigate S. mansoni egg deposition in the brain with hepatosplenic and cardiopulmonary forms of infection, respectively. They have observed that the frequencies of brain involvement in the cardiopulmonary form and the hepatosplenic form reduce from 61% to 41.1%, and from 26% to 12.7%, respectively, although the incidences are still high. It is inferred that at a higher rate of cardiopulmonary egg deposition, together with portal hypertension, eggs can easily reach the CNS via the cardiovascular system. The lack of symptoms is attributed to the earlier diagnosis by MRI and the efficacy and punctuality of anti-schistosomal treatment, such as praziquantel, in all susceptible species. The worms are then killed, and egg production, deposition and circulation in the vessels are all declined. Another reason is the sparse distribution of the eggs and a less intense periovular inflammatory reaction[5,8,18,26,27]. Zhou[28] has observed the schistosomula migration in the host, and reports that the schistosomula stay in pulmonary system before ectopic migration. Then they travel between cardiopulmonary and hepatosplenic systems for maturation. After that, they pair up and shed eggs, increasing the chance of invasion into the CNS. Warren *et al.*[29] have studied the schistosomiasis epidemiology, pathology and autopsy. They report that there are connections between egg burden and the number of worms in the host. Also, they relate the clinical symptoms and hepatosplenic pathology to the intensity of infection. Thus, it is proposed that the chronic schistosomiasis patients with liver cirrhosis and portal hypertension would be more easily infected[30]. However, the fact is totally different. Actually, NS often occurs in the early stage of schistosomiasis. Many researchers[6,11,16] have reported that NS is detected in the early stage of infection, with or without only mild hepatosplenic and intestinal symptoms. Kane and

Most[8,11] report that it usually takes 4 months for the appearance of NS after the first schistosomal infection. Ferrari has reported that acute neurological manifestation of S. mansoni infection may develop in non-immune individuals, such as tourists, 6-8 weeks after the onset of infection[5]. By observing the patients with chronic severe schistosomiasis mansoni, Pittella[30] conclude that the main factors for the high frequency of schistosomiasis egg deposition in the CNS include the large number of schistosomiasis eggs, continuous egg production, portal hypertension, and accumulation of pulmonary arteriovenous shunts or portopulmonary anastomoses.

According to the acute or chronic infection of S. mansoni, the different pathways, and other clinical findings, NS is divided into 2 stages. The first stage is the early infection or mild chronic hepatosplenic and intestinal infections. During this period, the eggs reach the CNS via the vertebral venous Batson's plexus, and the adult worms can also get close to the CNS to lay eggs. S. japonicum and S. mansoni usually parasitize in the inferior and the superior mesenteric veins to lay eggs. The eggs and adult worms then access the vertebral Baston's plexus, through either the arteriovenous anastomosis or vascular mutual shunts. However, S. haematobia usually pass through portosystemic anastamoses to reach the veins surrounding the urinary and the reproductive systems, which could also join the pelvic plexus retrograde flow to the CNS[31,32]. The second stage is the chronic severe infection. During this period, S. mansoni spinal cord symptoms are more common, such as myeloradiculopathy. The lack of neuropathic symptoms of cerebral schistosomiasis may be due to the sparse distribution of eggs in the brain, or the less intense granulomatous reaction around the eggs than that during acute schistosomiasis[5,18,33]. As a result of the portal hypertension and the pathway of the vertebral venous Batson's plexus, it is easier to open the above-mentioned pathways by vascular anastomosis, and the eggs can easily reach the CNS via the artery system, either through the pulmonary arteriovenous anastomoses or portal venous anastomosis such as the azygos vein. Most of these consequences are based on the formation of portal hypertension[33]. Other researchers speculate that the worms or the eggs could also invade the artery system under conditions of cardiac ventricular septal defect or patent foramen ovale. However, although this can be theoretically explained, the possibility is very small. Moreover, most of these deformations would be non-functional, without any blood flow[9,13].

4 Conclusion

In conclusion, a large number of schistosomiasis eggs, surrounded by granulomatous reaction, lodge together in the circumscribed areas of the CNS, and induce damage by both mass effect and inflammation itself. The eggs in the host tissues contain miracidia that release antigenic substances such as glycolipids, glycoproteins and metabolites, and function as antigens to elicit a strong delayed type hypersensitivity reaction. With the impairment of the blood-brain barrier, the eggs probably reach the CNS in the early period of infection and during chronic infection[33]. Due to the differences in schistosomiasis species, sizes of the eggs and stages of infection, the pathways of CNS invasion can be different. Fortunately, with the development of new scientific techniques such as MRI, the establishment of novel radioisotope tracer method, the improvement of medical skills, and various valuable experimental models, it is entirely possible that the pathogenesis of NS can be clearly revealed, and NS can be effectively prevented and treated.

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中枢神经系统血吸虫入侵途径研究进展

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摘要：血吸虫感染中枢神经系统的症状或有或无。当中枢神经系统血吸虫病呈现出明确症状时，其往往是血吸虫感染最为严重的表现之一。脑型血吸虫病以日本血吸虫感染为主，而脊髓型血吸虫病则以曼式血吸虫感染为主，同时也有埃及式血吸虫感染。关于中枢神经系统血吸虫病虫卵入侵途径，目前主要存在虫卵栓塞和成虫产卵两种学说，前者分为动脉栓塞、静脉栓塞和 Batson 椎静脉途径，成虫亦可循上述途径入侵中枢神经系统产卵。由于血吸虫种属以及机体感染阶段的差异，血吸虫进入中枢神经系统的途径亦有所不同。此外，肝硬化门脉高压在其入侵过程中也起重要作用。本文对中枢神经系统血吸虫病入侵途径的研究进展作一综述。

关键词：血吸虫；中枢神经系统血吸虫；中枢神经系统；途径；肉芽肿；发病机理