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Mini-Review

Helminthic invasion of the central nervous system: Many roads lead to Rome

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ABSTRACT

Invasion of the central nervous system (CNS) by parasitic worms often represents most severe complication of human helminthiasis. The pathways from the portal of entry to the CNS are manifold and differ from species to species. In this mini-review, we analysed the contemporary knowledge and current concepts of the routes pathogenic helminths take to gain access to brain, spinal cord and subarachnoid space.

Contents

1. Introduction

Infestation of the central nervous system (CNS) by parasitic worms or their larvae is a well-recognized and often most severe complication of human helminthiasis. Neurocysticercosis, a CNS infection by the larva of *Taenia solium*, is the world-wide leading cause of epilepsy [1,2], contributing to high mortality and morbidity in endemic areas in South America, Africa and South East Asia [3,4]. In Thailand, infection with *Gnathostoma* spp. has been shown to cause subarachnoid and intracerebral haemorrhage [5]. Focal and secondary generalized seizures are typical presentations of *Schistosoma japonicum* infection [6]. Symptomatic CNS involvement occurs in up to 4.3% of all cases [7] and the prevalence of epilepsy in endemic areas in the Far East Asia has been shown to be eight times as high as at the baseline [8]. In Brazil, it has been estimated that more than 5% of cases presenting with an inflammatory myelopathy were due to *Schistosoma mansoni* infection [9,10]. In one study from Malawi, as many as 50% of all non-traumatic myelopathies treated in a rehabilitation hospital were presumed to be spinal schistosomal infections [11]. *Angiostrongylus cantonensis* is a common cause of eosinophilic meningitis, which is endemic in many areas of Pacific basin [12,13]. Furthermore, CNS involvement has been well documented in echinococcal hydatid disease [14,15], sparganosis [16,17], coenurosis [18,19], paragonimiasis [20], strongyloidiasis [21,22], toxocariasis [23–26], lagochilascariasis [27], baylisascariasis [28] and cerebrospinal gnathostomiasis [29–32]. Table 1 summarizes helminths that cause CNS infections, their typical clinical presentations as well the frequency of the CSF involvement.

Only *A. cantonensis* is usually considered to be a neurotropic helminth as a passage through the subarachnoidal space is essential

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Table 1
Parasitic worms potentially invading the CNS.

Helminths	Common localization within the nervous system	Main clinical presentation	Frequency of the CNS involvement	Ref.
Trematodes				
Schistosoma spp.	Spinal cord (esp *S. mansoni* and *S. haematobium*), brain parenchyma (esp *S. japonicum*)	Painful subacute myelopathy, focal seizures	Common	[8]
Paragonimus spp.	Cerebral hemispheres, predominantly unilateral	Focal neurological deficits, focal seizures	Rare	[20]
Cestodes				
Cysticerus (Larva of *Taenia solium*)	Cerebral cortex, basal ganglia, Sylvian fissure, basal cisterns, ventricles	Focal seizures, intracranial hypertension	Very common	[1]
Sparganum (Larva of *Spirometra* spp.)	Cerebral hemispheres, predominantly unilateral	Focal seizures	Common	[17]
Coenurus (Larva of *Taenia multiplex*)	Cerebral hemispheres, cisterns, ventricles	Focal seizures, intracranial hypertension	Common	[19]
Echinococcus spp.	Cerebral hemispheres	Intracranial hypertension, focal seizures	Very rare	[14]
Nematodes				
Angiostrongylus cantonensis	Subarachnoid space	Eosinophilic meningitis	Nearly 100%	[13]
Gnathostoma spp.	Spinal cord, brain, subarachnoid space	Painful radiculomyeloencephalitis, eosinophilic haemorrhagic meningitis	Rare	[12]
Strongyloides stercoralis	Subarachnoid space	Hyperinfection-associated bacteriaemia and meninigitis	Rare	[22]
Animals ascarids: *Toxocara* spp. *Ascaris suum* *Baylisascaris procyonis* *Lagochilascaris minor*	Brain, spinal cord, subarachnoid space	Focal neurological deficits, focal seizures, myelopathy, eosinophilic meningitis, encephalopathy	Rare	[21,25,27,28,44]

for the completion of its life cycle in its natural host, the rat [13,33,34]. In all other helminths, their appearance in the subarachnoid space or central nervous system (CNS) is regarded as accidental. The pathways from the portal of entry of helminthic parasites (usually by ingestion or by skin penetration) to the CNS differ from species to species. In this review, we analysed the contemporary knowledge and current concepts of the routes of neurohelminthic infections and migratory pathways of the relevant parasitic worms based on clinical data, results of cerebrospinal imaging as well as our understanding of the specific biological features of the parasites.

2. Principal routes of CNS invasion

Helminths can spread to the CNS (1) via the systemic circulation (haematogenous spread) penetrating blood brain barrier in parenchymal microvessels or blood-cerebral spinal barrier in choroid plexus, (2) through the loose connective tissues of the skull and intervertebral foramina (Fig. 1), and (3) via the Batson's paravertebral venous plexus (Fig. 2). The first two routes are utilized by various parasites, while the retrograde migration through the Batson's plexus seems to be unique for the venous blood-dwelling *Schistosoma*. Table 2 summarizes the principal routes of brain, spinal cord and subarachnoid space invasion by parasitic worms.

2.1. Haematogenous spread to the brain and spinal cord

This mode of infestation is common in *Cysticercus*, *Echinococcus*, *Strongyloides*, *Toxocara* and *Angiostrongylus* infections. The eggs or larvae of these parasites are ingested and then penetrate the intestinal wall, reaching the portal vein and then the systemic circulation. In *Strongyloides stercoralis* infection, the infective filariform larvae penetrate the skin and directly enter the subcutaneous venous system. Except for *Angiostrongylus* spp., other helminths mentioned above are non blood-dwelling parasites. Nevertheless, the larval stages of these parasites are well-adapted to live in the circulation, due to their small size and their metabolism: As opposed to the adults in the intestine larval nematodes can utilize aerobic energy metabolism [35]. Migration to the lung via the blood stream is a natural part of the life cycle of *Strongyloides* spp. and *Toxocara* spp. After entering the circulation, larvae can cause “embolic” lesions in the liver and lungs and also in the brain and spinal cord. The larvae are typically found in the well-perfused areas of the brain as implied by frequent cortical distribution of cysticerci on cerebral imaging [36] as well as cortical or juxtacortical location of *Toxocara* abscesses [37–40].

In addition to *Toxocara* spp. various animal ascarids larvae can haematogenously spread to the CNS. In North America *Baylisascaris procyonis*, an ascarid of racoons, can cause severe eosinophilic meningoencephalitis in infants and young children [41]. *Ascaris suum* was shown to cause both encephalitis and myelitis in adult patients [42–44].

Disseminated asymptomatic and symptomatic cerebral involvement is common in *S. japonicum* infection, particularly if hepatic disease is present [45,46]. The disseminated deposition of eggs resulting in multifocal granulomatous lesions in the liver and/or intestine facilitates haematogenous spread more easily [47,48]. The hepatic disease concurrent with portal hypertension is thought to augment the dissemination of eggs through portopulmonary anastomoses to the pulmonary veins and then the systemic circulation. The eggs of *S. japonicum* are smaller than of *Ss. mansoni et haematobium* and lack a prominent spine. These features might facilitate their journey through the systemic circulation.

2.2. Direct invasion of the central nervous system

Sparganum (larva of the cestode *Spirometra* spp.), adult worms of lung fluke *Paragonimus* spp. and the larvae of *Gnathostoma* spp. have been shown to invade the CNS directly through the loose connective tissues of the neural foramina of the skull base and intervertebral foramina of the spine along the cranial and spinal nerves and vessels. These parasites are highly invasive mechanically by their active movements. Furthermore, those invasive parasites release a wide variety of molecules into their surrounding environment, that facilitate tissue penetration and invasion [49]. Among various components of these so-called excretory–secretory products, proteases are the major molecular species, both quantitatively and qualitatively [50]. For example, cystein protease has been shown to play a major role in tissue penetration by *Paragonimus westermani* [51]. Apart from cysteine proteases, matrix metalloproteinases (MMPs) play a key role in invasion of host tissues, as seen in the *Gnathostoma* spp. [52]. The understanding of the molecular mediators