CHAPTER 12

Helminth Infections of the Central Nervous System Occurring in Southeast Asia and the Far East

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Abstract

Although helminth infections of the central nervous system (CNS) are rare, their public health implications must not be neglected. Indeed, several helminth species can cause cerebrospinal infections, especially if humans serve as intermediate or non-permissive host. The diagnosis of cerebrospinal helminthiases is difficult, and the detection of parasites in cerebrospinal fluid is rarely successful. Cerebrospinal helminth infections therefore often remain undetected, and hence prognosis is poor. Increases in tourism and population movements are risk factors for cerebrospinal helminthiases and infections pose particular challenges to clinicians in non-endemic areas. In this review, we focus primarily on food-borne helminthiases that are endemic and often emerging in Southeast Asia and the Far East, namely angiostrongyliasis, gnathostomiasis, sparganosis, paragonimiasis and cysticercosis. Additionally, we discuss neuroschistosomiasis, a disease that is transmitted through human–water contact. For each disease, we describe the pathogen, its transmission route and possible mechanisms for entering the CNS. We also summarise common signs and symptoms, challenges and opportunities for diagnosis, treatment, clinical management, geographical distribution and epidemiology. The adoption of a comprehensive set of diagnostic criteria for different cerebrospinal helminthiases is proposed, including epidemiological history, typical signs and symptoms, neuroimaging and laboratory findings. Finally, risk factors, and research needs for enhanced patient management and population-based control measures are discussed.

12.1. INTRODUCTION

The majority of parasitic worms (helminths) fall into two groups: Nematoda, comprising the nematodes (roundworms), and Platyhelminthes, comprising the trematodes (flukes) and the cestodes (tapeworms) (Muller, 2002). To date, more than 340 helminth species have been identified in parasitic associations with humans, with a fair number of them probably representing cases of pseudoparasitism or accidental infection (Cox, 2002; Crompton, 1999). A few dozen species exert a considerable impact on human health and well-being.

Nematodes are transmitted via soil where their eggs and larvae reside (e.g. *Ascaris lumbricoides*, *Trichuris trichiura* and the hookworms), or by biological vectors such as mosquitoes (e.g. lymphatic filariasis), and intermediate host snails (e.g. angiostrongyliasis), freshwater fish (e.g. gnathostomiasis) and mammals (e.g. trichinellosis). Soil-transmitted helminth infections are the most common nematodes in the world, with particularly high prevalences reported from the tropics and subtropics (Bethony et al., 2006; de Silva et al., 2003; Hotez et al., 2007). Food-borne nematode infections are comparatively rare, but outbreaks are common for some species, such as *Trichinella spiralis* (Liu and Boireau, 2002) and *Angiostrongylus cantonensis* (Lv et al., 2008), and cause considerable morbidity. Many nematode species can invade the central nervous system (CNS) via the bloodstream. Angiostrongyliasis, gnathostomiasis, strongyloidiasis, toxocariasis and baylisascariasis are some of the most common infections of the CNS and the former three are prevalent in Southeast Asia.

With a few exceptions, trematodes rely on aquatic snails as their first intermediate hosts (Gryseels et al., 2006; Keiser and Utzinger, 2009). In the case of food-borne trematodiases, cercariae either encyst on aquatic vegetation, or penetrate the skin of a second intermediate host (e.g. fish and frogs) where they encyst (Keiser and Utzinger, 2009). Humans acquire an infection through the consumption of contaminated raw water plants (*Fasciola* spp.) or insufficiently cooked freshwater fish and other aquatic products. In view of the exponential growth of aquaculture, food-related trematode infections have gained in importance in many parts of the world (Keiser and Utzinger, 2005). With the exception of the lung fluke *Paragonimus*, with one report from the People's Republic of China (P.R. China) indicating that 9.8–19.7% of hospitalised patients had developed cerebrospinal paragonimiasis (Zhao, 1994), other trematodes seldom enter the CNS. Regarding schistosomiasis, it has been reported that the eggs of *Schistosoma japonicum* can lead to CNS involvement (Liu, 1993).

Adult cestodes exclusively parasitise the intestines of their definitive host, while the larvae reside in different locations in the intermediate host. Humans acquire an infection through the consumption of larvae-infested

intermediate or paratenic hosts, or become intermediate hosts when accidentally ingesting worm eggs. Some species also rely on direct transmission or vectors. Negative health effects due to adult cestodes are minimal and mainly due to the competition for nutrients. However, larvae often induce severe disease if they end up in an accidental host. Cysticercosis caused by the cysticercus of *Taenia solium* and echinococcosis caused by the metacestodes of *Echinococcus* spp. are the most important human larval cestodiases. Neurocysticercosis (NC), as the most severe form of cysticercosis, is the leading cause of acquired epilepsy (García and Del Brutto, 2005; Roman et al., 2000). Cerebral sparganosis caused by the migration of sparganum of *Spirometra* is relatively rare, but can be of local importance in Southeast Asia and the Far East, and is linked to specific cultural and dietary habits.

The human CNS does not constitute a definitive location for any helminth species but is occasionally and mostly accidentally reached during the migration of helminth larvae and eggs in the human body, especially if humans serve as intermediate or non-permissive hosts. However, some species show neurotropism if they accidentally end up in humans, such as the larvae of *A. cantonensis* and *T. solium*. With a few exceptions of ocular and nasal involvement, almost all angiostrongyliasis cases due to *A. cantonensis* infection involve the CNS (Wang et al., 2008). As many as 91.0% (7889/8674) of all cysticercosis inpatients in the mainland of P.R. China show cerebrospinal involvement (Wang, 2008). Usually, helminths invade the CNS via two routes: either the bloodstream or migration through soft tissue. For the larvae of most nematodes (e.g. *A. cantonensis* and *Toxocara* spp.) and some tapeworms (e.g. *T. solium* and *Echinococcus* spp.) the bloodstream is the main avenue to the CNS. Infrequently, the eggs of *Schistosoma* spp. can also be carried to the CNS via the blood (Gryseels et al., 2006). Larvae of other species may migrate to the CNS along nerves, vessels and muscles (e.g. *Gnathostoma* spp., *Spirometra mansoni* and *Paragonimus westermani*) (Oh, 1968a; Punyagupta et al., 1990).

An infection of the CNS with helminths can be disabling and fatal if left untreated. The diagnosis of cerebrospinal helminthiases is difficult since larvae or worms can seldom be recovered and symptoms are unspecific. Eosinophil cells in the cerebrospinal fluid (CSF) can serve as an indicator for helminth infection of the CNS but they are not necessarily always present over the course of an infection. Neuroimaging techniques can reveal lesions in the CNS, but the manifestations are often nonspecific and typical imaging features are lacking in most patients. Therefore, misdiagnosis due to signs and symptoms common for other diseases (e.g. tuberculosis and intracranial cancers) is widespread, particularly outside known endemic areas.

Cerebrospinal helminthiases are often neglected in disease control programmes because they are not a primary clinical form for most

helminth infections. However, some emerging risk factors call for more attention to cerebrospinal helminth infections. Large population movements and expanding international tourism place people from non-endemic areas at risk of acquiring a disease and thus pose challenges to clinicians in non-endemic areas (Gushulak and MacPherson, 2004). Immunocompromised individuals (due to AIDS, chronic diseases or use of immunosuppressants) are at a higher risk of cerebral involvement, for example in the case of a *Strongyloides stercoralis* infection (Walker and Zunt, 2005).

In this review, we focus on cerebrospinal helminthiases with particular consideration of those commonly occurring in Southeast Asia and the Far East. Food-borne trematode infections are an emerging public health issue in Southeast Asia and the Far East, partially explained by rapidly expanding aquaculture, and diversification and long-distance distribution of food resources. Angiostrongyliasis, gnathostomiasis, sparganosis and paragonimiasis are typically associated with aquatic products such as freshwater fish, snails, frogs, snakes, crabs and crayfish. Rapidly increasing consumption of pork imposes new risks for cysticercosis, especially in rural areas. Considerable progress has been made in the control of Asian schistosomiasis, but in view of its public health importance and the risk of re-emergence due to climate change, it is also discussed. Key features of the main cerebrospinal helminthiases, including causative agents, risk factors, common signs and symptoms and differential diagnosis are summarised in Table 12.1.

12.2. ANGIOSTRONGYLIASIS

12.2.1. Pathogen

Human angiostrongyliasis is primarily caused by *A. cantonensis* and *A. costaricensis*. The former is also known as rat lungworm and is the most important aetiological agent of eosinophilic meningitis (Graeff-Teixeira et al., 2009). *A. cantonensis* was first discovered in 1933 during the examination of *Rattus norvegicus* (brown rats) and *R. rattus* (black rats) in Guangzhou, P.R. China (Chen, 1935). The first human infection was reported from Taiwan in 1945, but the public health significance was not recognised until the 1960s (Cross, 1987), when the parasite was recovered from a Filipino patient in Hawaii (Rosen et al., 1962) and an epidemic was identified on some Pacific islands (Rosen et al., 1967). *A. costaricensis* mainly causes eosinophilic infiltrations in the intestinal wall, especially the ileocecal region (Loria-Cortes and Lobo-Sanahuja, 1980). Two other species, namely *A. malayiensis* in Southeast Asia and *A. mackerras* in Australia, have been suspected as the causes of neurological lesions in

TABLE 12.1 Summary of main cerebrospinal helminth infections in Southeast Asia and the Far East

Disease	Causative agent(s)	Main occurrence in Eastern Asia	Risk factors	Signs and symptoms	Laboratory findings	Neuroimaging	Main differential diagnosis	Treatment
Angiostrongyliasis	*Angiostrongylus cantonensis* (larva)	P.R. China, Japan, Thailand, Vietnam, etc.	Eating raw or undercooked snails, slugs, frogs, crustaceans and lizards. In Western hemisphere, consumption of raw vegetables contaminated by snail or slug secretions or egg masses	Meningitis (severe headache, nausea, vomiting, neck stiffness, paraesthesia, fever, etc.); meningoencephalitis (headache, pain in trunk); radiculomyelitis (pain in trunk and extremities)	Eosinophilia and larvae in CSF; eosinophilia in peripheral blood	Compatible with meningitis	Gnathostomiasis, cysticercosis, paragonimiasis, schistosomiasis, meningitis caused by tuberculosis, viral meningitis	Chemotherapy (albendazole and mebendazole); anti-inflammatory treatment (corticosteroids)
Neurognathostomiasis	*Gnathostomus spinigerum*, *G. hispidum*, *G. nipponicum*, *G. doloresi* (larva)	Thailand	Eating raw or undercooked fish (swamp eel), frogs, snakes, birds; drinking untreated water	Radiculomyelitis (a sudden radicular pain and/or headache, followed by paralysis of the extremities and/or cranial nerve palsies); encephalitis (headache, disturbance of consciousness and cranial nerve palsies); radiculomyeloencephalitis Manifestation outside CNS: subcutaneous migratory swellings with haemorrhage	Xanthochromia and eosinophilia in CSF, larvae during biopsy; eosinophilia in peripheral blood	Cord enlargement and diffuse high-signal intensity; haemorrhagic tract and scattered deep intracerebral haemorrhage with diffuse, fuzzy white matter lesions in brain	Angiostrongyliasis, sparganosis, schistosomiasis, intraspinal tumor	Surgery; chemotherapy (albendazole and ivermectin); anti-inflammatory treatment (corticosteroids)

Neurocysticercosis	*Taenia solium* (cysticercus)	P.R. China, Indonesia, Malaysia, Thailand, Vietnam, Lao PDR	Eating raw or undercooked vegetables and plant food; contact with tapeworm carriers	Mass effect (seizure); meningoencephalitis (headache, vomiting, diplopia, papilloedema, etc.) Manifestation outside CNS: subcutaneous swellings		A viable cyst presents a ''hole-with-dot''; a degenerating cyst appear as contrast-enhancing rings or nodules surrounded by oedema; a calcified cyst appear as hyperdense dots or areas of subtracted signal	Intracranial tumours, sparganosis, paragonimiasis	Chemotherapy (praziquantel and albendazole); anti-inflammatory treatment (corticosteroids); antiepileptic drugs and surgery
Neruosparganosis	*Spirometra mansoni* (sparganum)	P.R. China, Thailand, Korea, Japan	Eating raw or undercooked frog/tadpole, snake; drinking raw snake blood or bile, or untreated water; using poultice of frog flesh	Seizures, hemiparesis, headache Manifestation outside CNS: subcutaneous migratory swellings	Sparganum during biopsy, eosinophilia in peripheral blood	Tunnel sign and multiple conglomerated ring or bead-shaped enhancements	Metastatic brain tumours	Surgery
Neuroparagonimiasis	*Paragonimus westermani*, *P. skrjabini*, *P. heterotremus*, *P. miyazakii*, *P. ohirai* (worm or egg)	P.R. China, Vietnam	Eating raw or undercooked crab or crayfish	Eosinophilic meningitis (headache, fever, vomiting); seizure, arachnoiditis, mass effects (paralysis) Manifestation outside CNS: subcutaneous migratory swellings, coughing and rusty sputum for a long time	Xanthochromia in CSF; eggs in sputum; eggs or worms during biopsy	Clustered ring-enhancing lesions	Sparganosis, tuberculosis	Chemotherapy (triclabendazole and praziquantel); anti-inflammatory treatment (corticosteroids); surgery

(*continued*)

TABLE 12.1 (*continued*)

Disease	Causative agent(s)	Main occurrence in Eastern Asia	Risk factors	Signs and symptoms	Laboratory findings	Neuroimaging	Main differential diagnosis	Treatment
Neuroschistosomiasis	*Schistosoma japonicum*, *S. mekongi* (egg)	P.R. China, Philippines, Indonesia, Lao PDR, Cambodia	Contact with freshwater in endemic area	Encephalitis and/or meningitis (headache, vomiting, speech disturbances, disorientation, visual abnormality, urinary incontinence, etc.); tumoral form (seizures accompanied by the loss of consciousness; headache, visual abnormality, sensory disturbance, hemiparesis, etc.) Manifestation outside CNS; Katayama syndrome	Eggs in faeces; eggs during biopsy	Multiple clustered, enhanced nodules	Intracranial tumours (brain glioma), epilepsy due to other causes	Chemotherapy (praziquantel); anti-inflammatory treatment (corticosteroids); surgery

humans (Cross, 1987; Prociv et al., 2000). However, thus far, the worms have not been isolated from patients.

Adult *A. cantonensis* worms parasitise the pulmonary arteries and cardiac cavities of rats and release their eggs into the bloodstream. After hatching, the larvae penetrate the capillary walls in the lung tissue and enter the airways. The first-stage larvae (L_1) in the rat sputum are then swallowed and pass the intestine to be released with the faeces. The free larvae enter their mollusk intermediate hosts (i.e. snails or slugs) upon which they develop into third-stage infective larvae (L_3). Various animals (e.g. frogs, shrimps, crabs, fish and lizard) can serve as paratenic hosts in which the infective larvae can live several weeks without further development (Wallace and Rosen, 1966, 1967). When rats ingest intermediate or paratenic hosts harbouring infective larvae, the larvae penetrate the stomach or intestinal walls and migrate through the host body.

A. cantonensis is neurotropic; that means the larvae stay in the CNS where they further grow and develop. Within approximately 4 weeks and after two molts, worms penetrate the cerebral vein and migrate to the heart and pulmonary arteries. Adult worms mate and deposit the first eggs approximately 5 weeks post-infection.

Humans are non-permissive hosts for this nematode. The larvae can invade the human CNS via the bloodstream, but usually fail to pass through the cerebral vessels and enter the pulmonary arteries. In children, the larvae may enter the pulmonary vessels and induce potentially fatal inflammation in the lung, but sexually mature adult worms are seldom found. Infections occur when raw or undercooked freshwater or terrestrial snails and slugs, paratenic hosts or contaminated vegetables are consumed.

12.2.2. Clinical manifestations

A. cantonensis induces inflammation in neural tissues and usually increases eosinophil cell counts, a syndrome known as eosinophilic meningitis. The incubation period of eosinophilic meningitis is variable, ranging from 1 day to several months. In an angiostrongyliasis outbreak that could be linked to the consumption of the terrestrial snail *Achatina fulica*, typical clinical symptoms appeared within 1–6 days (Kliks et al., 1982). However, in a large outbreak which occurred in Beijing in 2006, involving 160 patients, the incubation period in 128 patients (80%) was 7–36 days with a median of 14 days (He et al., 2007). This outbreak was linked to the consumption of *Pomacea canaliculata* snails, a freshwater species. The estimated mean incubation period among 33 patients in a recent outbreak in Dali, P.R. China, which was due to the consumption of raw *P. canaliculata* snails, was 16 days with a range of 3–50 days (Lv et al., 2009a). The latent period was as long as 54 days (standard deviation: 30 days) in an

outbreak due to drinking raw vegetable juice (Tsai et al., 2004). These outbreaks indicate that the incubation period might be associated with the number of ingested larvae.

Different clinical manifestations of angiostrongyliasis have been described. Eosinophilic meningitis is the main clinical entity associated with the disease (Sawanyawisuth and Sawanyawisuth, 2008). Other clinical manifestations include eosinophilic meningoencephalitis (Furugen et al., 2006), eosinophilic radiculomyelitis (Schmutzhard et al., 1988), ocular angiostrongyliasis (Sinawat et al., 2008) and, more rarely, nasal (Liu and An, 2000) or pulmonary infections (Li et al., 2001; Lindo et al., 2004). Most infections are self-limiting and recovery is without sequelae (Punyagupta et al., 1975; Yii, 1976). However, illness developing into encephalitis may be fatal (Sawanyawisuth and Sawanyawisuth, 2008). Less than 10% of all patients infected with *A. cantonensis* develop encephalitis, but among them a lack of effective treatment results in high mortality (Sawanyawisuth and Sawanyawisuth, 2008).

Cerebrospinal inflammation and resulting increased intracranial pressure is the primary pathology of angiostrongyliasis. The most common complaint of patients is acute and deteriorating headache as a result of increased intracranial pressure (Graeff-Teixeira et al., 2009). Headache may be accompanied by nausea and vomiting. Approximately 40% of all patients experience neck stiffness and paraesthesia (Wang et al., 2008), which usually lasts for less than 2 weeks and affects different locations (usually the extremities). It has been described as hyperaesthesia, itching or a sensation of worms crawling under the skin (Wang et al., 2008). Less common symptoms include pain in the trunk or extremities, facial paralysis, blurred vision or diplopia. Fever is mostly absent in adults while paediatric patients are often highly febrile (Hwang and Chen, 1991). Children suffer more often from neck stiffness, nausea, vomiting, somnolence and abdominal pain (Hwang and Chen, 1991).

12.2.3. Diagnosis

The recovery of larvae from CSF or the ocular chamber is the definitive proof for human angiostrongyliasis. However, in a recent review of case reports and outbreaks occurring in the mainland of P.R. China between 1979 and 2006, only 16 patients (4.8%) out of a total of 334 cases were parasitologically diagnosed (Lv et al., 2008). In Thailand, none of the 484 cases reported there revealed parasites in the CSF (Punyagupta et al., 1975). The chance of diagnosing a child parasitologically is higher than for adults; the larval recovery rate from CSF by lumbar puncture was as high as 41.5% among paediatric cases in Taiwan (Hwang and Chen, 1991). In another survey involving 125 individuals, 8 out of 9 parasitologically confirmed cases were younger than 8 years (Yii, 1976). A clinical

angiostrongyliasis diagnosis is often made based on eating history, clinical symptoms and diagnostic work-up. Specifically, a history of eating freshwater or terrestrial mollusks, paratenic hosts or potentially contaminated vegetables is crucial for clinical diagnosis.

Eosinophilia is an important indicator for helminth infections. An elevated eosinophil cell count (>10% of total white blood cells or >500 cells/μl) in CSF is of specific relevance for angiostrongyliasis due to the frequent involvement of the brain (Lv et al., 2009a; Punyagupta et al., 1970; Slom et al., 2002). However, not each examination of an angiostrongyliasis case shows eosinophilia in the CSF, since the counts may vary over the course of infection (Lv et al., 2009a; Punyagupta et al., 1975). Another diagnostic approach is immunological testing for antibodies or specific antigens from *A. cantonensis* in peripheral blood and CSF (Dorta-Contreras et al., 2005; Slom et al., 2002; Tsai et al., 2001b). Several tests including enzyme-linked immunosorbent assay (ELISA) and immuno-polymerase chain reaction (PCR) have been developed but reported sensitivities and specificities are questionable due to small sample sizes. At present, no commercially available kit for diagnosing angio-strongyliasis is on the market (Wang et al., 2008).

Categorised diagnosis based on the strength of clinical and epidemiological evidence was recently proposed (Lv et al., 2009a). Although *A. cantonensis* is generally regarded as the leading agent for eosinophilic meningitis, other causes must be considered to strengthen differential diagnosis. Hence, thorough diagnostic work-up and differential diagnosis are important in areas such as Southeast Asia and the Far East where special food items (e.g. snails, frogs, snakes and raw fish) are popular and other parasites causing eosinophilic meningitis co-exist. For example, both *A. cantonensis* and *Gnathostoma spinigerum* contributed to an epidemic of eosinophilic meningitis in Thailand (Punyagupta et al., 1975, 1990).

12.2.4. Treatment and clinical management

The severity of human angiostrongyliasis varies from mild and self-limiting to fatal, depending on the parts of the brain involved and the worm burden. The clinical management of angiostrongyliasis includes administration of anthelminthic drugs, supportive measures and sometimes even surgery. Repeated lumbar puncture or mannitol transfusion is employed to relieve symptoms such as severe headache and vomiting by decreasing intracranial pressure (Chotmongkol et al., 2000; Lv et al., 2009a). Surgical removal of worms is the preferred method for the management of ocular angiostrongyliasis (Kumar et al., 2005; Malhotra et al., 2006; Sinawat et al., 2008; Toma et al., 2002).

The suitability of anthelminthics is controversial due to their potential to exacerbate inflammation (Bowden, 1981; Hidelaratchi et al., 2005). Still, albendazole and mebendazole are widely used against *A. cantonensis* in clinical practice (Sawanyawisuth and Sawanyawisuth, 2008). A trend to lower frequency of headache and a shorter mean duration of headache in the treatment group were reported from a randomised placebo-controlled trial assessing the efficacy of albendazole, but the statistical evidence was weak (Jitpimolmard et al., 2007). Two observational studies showed a satisfactory effect of albendazole in the treatment of children (Hwang and Chen, 1991; Lin et al., 2003b). Levamisole is another anthelminthic drug which has been used to treat children with reportedly good efficacy (Hwang, 1997). Thiabendazole showed no appreciable effect when the drug was administered at a dosage of 50 mg/kg/day for 3 days (Kliks et al., 1982). No clinical trial has assessed the efficacy of mebendazole alone. Corticosteroids have been confirmed to be useful, probably by decreasing inflammation (Chotmongkol et al., 2000; Sawanyawisuth and Sawanyawisuth, 2008; Tsai et al., 2004), but many relapses were reported (Sawanyawisuth et al., 2004a; Tsai et al., 2004). Currently, a combination of anthelminthic drugs and corticosteroids is recommended for the treatment of angiostrongyliasis patients (Chotmongkol et al., 2004, 2006).

12.2.5. Geographical distribution and epidemiology

Since 1945 when the first human angiostrongyliasis case was described, over 2800 cases have been documented in the literature; 77% of them in Southeast Asia, P.R. China and Japan (Wang et al., 2008). More than 30 countries or territories, mainly located in tropical and subtropical regions, have been identified as endemic (Kliks and Palumbo, 1992). All countries in Southeast Asia except Myanmar, Brunei and Timor Leste are considered endemic for *A. cantonensis*. Thailand is the most heavily endemic area; more than 1300 cases have been reported since the 1950s (Wang et al., 2008). Today, hundreds of suspected cases are reported every year, especially from northeastern Thailand (Eamsobhana and Tungtrongchitr, 2005). It is estimated that the annual incidence rate is approximately 2 per 100,000 in Thailand (Suankratay et al., 2001). Other countries including Vietnam, Cambodia, Indonesia and Malaysia reported sporadic cases. A total of 382 cases from nine provinces had been identified in the mainland of P.R. China by the end of 2008 (Deng et al., 2007; Lv et al., 2008, 2009a). Fifty-four cases were described in Japan before 2003 and 61.1% of all cases were found on Okinawa (Nawa, 2005). Many of the remaining infections probably originated from Okinawa or outside Japan (Nawa, 2005).

Considerable geographical heterogeneity with regard to prevalence among animal hosts has been found. For instance, two high-prevalence clusters located in Fujian province and Guangxi Zhuang autonomous region in P.R. China were identified when infection rates in *P. canaliculata* were surveyed (Lv et al., 2009b). At a smaller spatial scale, prevalence can decrease with the distance from the centre of the village (Li et al., 2006b). The host specificity of *A. cantonensis* is low. For example, natural infections have been found in 22 mollusk species and 11 different rodents (Lv et al., 2008). The first national survey in P.R. China revealed that *P. canaliculata* and *A. fulica* were the predominant intermediate hosts (Lv et al., 2009b), while *Pila* spp. was identified as the key intermediate host in Thailand (Tesana et al., 2008).

The prevalence of angiostrongyliasis in Southeast Asia and the Far East is strongly associated with eating habits deeply rooted in local culture. Freshwater and terrestrial snails, mainly *Pomacea* spp., *Pila* spp. and *A. fulica*, are the most common source of infection in this region (Lv et al., 2008; Punyagupta et al., 1970; Yii, 1976). Since the terrestrial snail *A. fulica* usually has a higher infection rate and worm burden than freshwater snails, the consumption of *A. fulica* often results in more severe manifestations and higher case numbers (Yii, 1976). Isolated cases are often attributed to freshwater snails (Lv et al., 2008; Tsai et al., 2001a) or terrestrial slugs, frogs and monitor lizards (Li et al., 2006a; Liu et al., 2006; Parameswaran, 2006). Living slugs are sometimes swallowed as part of traditional medicine treatments and might result in severe meningitis (Li et al., 2006a; Liu et al., 2006).

The epidemiological patterns of eosinophilic meningitis due to *A. cantonensis* in Southeast Asia and the south of P.R. China and Japan are changing. For example, the use of snails for rearing domestic animals was widely practiced in Taiwan in the 1970s (Yii et al., 1975) but is declining, and the importance of slugs in traditional medicine is diminishing. However, the spread of invasive snail species, tourism and the consumption of exotic foods have become driving factors in the epidemiology of angiostrongyliasis. The invasion of *P. canaliculata* in P.R. China may serve as an illustration. This freshwater snail was introduced around 1980, and is now well established in southern P.R. China (Lv et al., 2009b). Three quarters of the 382 cases and eight of nine outbreaks (each comprising at least six cases) of cerebral angiostrongyliasis have been attributed to this species (Deng et al., 2007; Lv et al., 2008, 2009a).

Travel is the common route of exposure to *A. cantonensis* for individuals from non-endemic countries (Deng et al., 2007; Malvy et al., 2008; Maretic et al., 2009; Slom et al., 2002; Tsai et al., 2001a). Long-distance food transportation is another important risk factor. The large outbreak in Beijing (non-endemic) in 2006 was attributed to snails imported from an endemic area.

12.3. GNATHOSTOMIASIS

12.3.1. Pathogen

Human gnathostomiasis is caused by the larval migration of at least four *Gnathostoma* species, namely *G. spinigerum*, *G. hispidum*, *G. doloresi* and *G. nipponicum* (Herman and Chiodini, 2009). The most common species parasitising humans is *G. spinigerum* (Rusnak and Lucey, 1993). First discovered in the stomach wall of a tiger that died in a zoological garden in London in 1836 (Graeff-Teixeira et al., 2009), *G. spinigerum* is now recognised as a common stomach parasite of cats and dogs, especially in Southeast Asia (Anderson, 2000). Although the first human case of gnathostomiasis (cutaneous migration) was reported from Thailand as early as 1889 (Herman and Chiodini, 2009), the first case with CNS involvement was only recognised in 1967 (Chitanondh and Rosen, 1967). Today, *G. spinigerum* and *A. cantonensis* are considered the two main agents for eosinophilic meningoencephalitis (Ramirez-Avila et al., 2009), with the mortality caused by the former far exceeding that due to the latter (Boongird et al., 1977; Punyagupta et al., 1990; Schmutzhard et al., 1988).

Adult *G. spinigerum* typically parasitise the stomach wall of carnivorous mammals. Eggs are passed to the environment via faeces and, upon reaching freshwater, hatch within 8–10 days to release L_1 (Rojekittikhun, 2002b). The free larvae are ingested by the first intermediate host, namely water fleas (copepods). They develop into second-stage larvae (L_2) and when infected copepods are ingested by a second intermediate host (e.g. fish, eels, frogs and reptiles), the larvae are released in the intestine and develop into L_3 which then migrate through the tissue and encyst in muscles of their hosts. Infective L_3 can also be passed from one host to another (paratenic host) via predation and scavenging. When ingested by a definitive host, L_3 are released in the gastrointestinal tract from where they migrate to the liver and abdominal cavity. Within approximately 4 weeks they return to the stomach and invade the gastric wall, resembling a tumour with an aperture in the gastric lumen through which eggs are released starting about 100 days post-infection (Miyazaki, 1960).

Humans are non-permissive definitive hosts of *G. spinigerum* and subcutaneous or visceral migrating larvae are more frequently found than adult worms in the stomach wall. The mechanism of migration to the CNS is unclear, but based on the typical clinical picture, migration is likely to occur from nerve roots to the CNS (Boongird et al., 1977). The consumption of insufficiently cooked second intermediate hosts or paratenic hosts probably is the primary source of infection. Thus far, 48 vertebrate species have been found to be naturally infected with *G. spinigerum* in Thailand (Rojekittikhun, 2002b), suggesting a complex transmission route to humans. Drinking freshwater contaminated with

infected copepods has also been suggested as a route of infection (Punyagupta et al., 1990; Samarasinghe et al., 2002), in this case rendering humans to become second intermediate hosts rather than definitive hosts. However, it is unclear whether this route is associated with a higher risk of neurognathostomiasis (NG). Direct skin penetration of infective larvae and prenatal transmission have also been suggested (Rusnak and Lucey, 1993).

12.3.2. Clinical manifestations

The incubation period of NG is not known. Unlike the neurotropic *A. cantonensis*, *G. spinigerum* accidentally invades the CNS while the larvae migrate through the human body (Punyagupta et al., 1990). An outbreak of gnathostomiasis revealed that the most common clinical feature (i.e. migratory swellings and creeping eruptions) occurs within 20 days after consumption of raw fish and can repeatedly appear within 10 weeks (Chai et al., 2003). This probably indicates that migration lasts for several weeks and that the CNS can be involved at any time.

The main findings in CNS involvement are radiculomyelitis, radiculomyeloencephalitis and subarachnoid haemorrhage (Boongird et al., 1977; Punyagupta et al., 1990). Typical symptoms are a sudden onset of severe radicular pain and/or headache, followed by paralysis of the extremities and/or cranial nerve palsies (Boongird et al., 1977; Punyagupta et al., 1990). This clinical picture probably reflects the migratory pathway of the parasite, that is entering the spinal cord along nerve roots (Boongird et al., 1977). Radicular pain is extremely sharp, non-shooting or shooting along the nerve root, sometimes accompanied by a burning component. Severe pain can last from half an hour to a few hours and occurs several times each day (Punyagupta et al., 1990). Though not as frequent as in eosinophilic meningitis due to *A. cantonensis*, headache can appear when the cervical and cranial nerve roots are involved, or due to larval migration in cerebral tissue. The degree of paralysis varies from minimal weakness of the extremities to complete paralysis, depending on the migration pathway and the areas involved. Monoplegia, triplegia and quadriplegia have been observed, with paraplegia of lower limbs the most common. Cranial nerve palsies usually occur after paralysis of the extremities, which implies that the parasite tends to migrate from the lower spinal cord towards the brain. Multiple cranial nerve palsies usually indicate a poor prognosis. Urinary retention usually follows radiculomyelitis and radiculomyeloencephalitis.

In addition to pain and paralysis, other symptoms include neck stiffness, paraesthesia, fever, blurred vision and migrating swelling. Cutaneous gnathostomiasis accounts for the majority of patients infected with *Gnathostoma* but is rarely found in NG patients (Boongird et al., 1977;

Punyagupta et al., 1990). Hence, cutaneous migratory swelling is not considered important evidence for diagnosis. However, xanthochromic or bloody spinal fluid is characteristic of NG; more than 60% of all patients experience xanthochromic CSF (Boongird et al., 1977; Punyagupta et al., 1990). Over 12% of all patients with NG die due to extensive damage of vital centres in the brain stem or other complications (Boongird et al., 1977). The hallmark signs of gnathostomiasis are haemorrhagic tracts throughout the spinal cord and cerebral tissue post-mortem (Boongird et al., 1977; Bunnag et al., 1970; Punyagupta et al., 1990).

12.3.3. Diagnosis

Recorded outbreaks of gnathostomiasis following the consumption of raw fish suggest that only few patients present with symptoms associated with cerebrospinal involvement (Chai et al., 2003; Díaz Camacho et al., 2003). NG is diagnosed based on a combination of recent exposure history, symptoms and laboratory findings. A history of eating undercooked freshwater fish (e.g. swamp eels and loaches), frogs, snakes and chicken in endemic areas and drinking untreated water are risk factors for a *Gnathostoma* infection (Punyagupta et al., 1990; Samarasinghe et al., 2002). The typical clinical symptoms of NG mentioned above are essential for diagnosis, but other findings can be equally important. Although migratory swellings in subcutaneous tissue and eyelids only appear in about 4% and 7% of all NG cases respectively (Punyagupta et al., 1990), subcutaneous haemorrhage due to larval migration is characteristic of gnathostomiasis and thus important for differential diagnosis (Herman and Chiodini, 2009). The appearance of red blood cells is the hallmark sign of gnathostomiasis and crucial for diagnosis. Sometimes the larvae can be isolated from creeping eruptions (Chai et al., 2003).

Immunological tests for the diagnosis of NG have been developed (Anantaphruti, 2002), but tests with good sensitivity and specificity are still lacking and cross-reactivity with other parasitic infections remains a problem (Herman and Chiodini, 2009). Serological tests currently available for the diagnosis of gnathostomiasis include an assay based on crude somatic extracts of adult *G. doloresi* worms (Chai et al., 2003; Díaz Camacho et al., 2003), and an immunoblot technique to detect the specific 24-kDa band, which is widely used in Europe (Tapchaisri et al., 1991). However, no commercial reagents are currently available (Herman and Chiodini, 2009). Magnetic resonance imaging (MRI) and computed tomography (CT) are also used for diagnosis. Cord enlargement with diffuse high-signal intensity can indicate spinal gnathostomiasis (Sawanyawisuth et al., 2004b). Haemorrhagic tracts and scattered deep haemorrhage with fuzzy white matter lesions are found in cerebral gnathostomiasis (Sawanyawisuth et al., 2004b, 2009).

The main parasite to consider in differential diagnosis of NG is *A. cantonensis*. Angiostrongyliasis produces similar neurological manifestations, but acute severe radicular pain, signs of spinal cord compression and xanthochromic spinal fluid are uncommon (Ramirez-Avila et al., 2009; Schmutzhard et al., 1988). Freshwater fish may be paratenic hosts of *A. cantonensis* (Wallace and Rosen, 1967), but terrestrial or freshwater snails and slugs are more important sources of infection, especially in Southeast Asia and the Far East (Lv et al., 2008; Punyagupta et al., 1970). Thus, differential diagnosis should always consider the eating history. Another parasitic infection which must be ruled out in differential diagnosis is cerebral sparganosis caused by the sparganum of *Spirometra mansoni*.

12.3.4. Treatment and clinical management

To our knowledge, no effective treatment is available for *Gnathostoma* infections. Surgical removal of the larvae is effective in the management of subcutaneous infections and occasionally NG (Bunyaratavej et al., 2008). Various anthelminthic drugs (e.g. thiabendazole, praziquantel, metronidazole and diethylcarbamazine) and the antimalarial drug quinine have been assessed for their efficacy against gnathostomiasis both in animal studies and in humans, but failed to exhibit appreciable efficacy.

Currently, researchers focus on two widely used anthelminthics, albendazole and ivermectin. Poor absorption generally limits the deployment of albendazole for the treatment of tissue nematodes, but one clinical trial with this drug reported high cure rates in subcutaneous gnathostomiasis. The regimen of 400 mg once or twice daily for 3 weeks effectively reduced the frequency of symptoms and lowered eosinophil counts (Kraivichian et al., 1992). At present, there are insufficient data regarding its use in NG, although complete recovery was reported for some individuals treated with albendazole (Bunyaratavej et al., 2008; Germann et al., 2003). Ivermectin has been reported to be similarly effective as albendazole for the treatment of gnathostomiasis (Kraivichian et al., 2004; Nontasut et al., 2000, 2005). However, the sample sizes of previous studies involving ivermectin were small (17–21 subjects). Larger clinical trials assessing both efficacy and safety are needed. No obvious adverse events were reported but a potential issue is exacerbation of cutaneous symptoms. In a clinical trial, more patients treated with ivermectin than patients receiving albendazole experienced local skin reactions during the first week after drug administration (Kraivichian et al., 2004), raising concerns that ivermectin treatment of patients with ocular and CNS involvement might be unsafe (Herman and Chiodini, 2009).

Corticosteroids have been successfully used to prevent inflammation in cerebrospinal tissue due to angiostrongyliasis and neurocystercercosis

(Chotmongkol et al., 2000; García et al., 2002). One observational study involving gnathostomiasis patients failed to show conclusive results. The symptoms did not significantly improve in 118 out of 162 patients with NG after the administration of oral prednisolone at 40–60 mg daily or intravenous dexamethasone at 5 mg every 4–6 h (Punyagupta et al., 1990). This failure could be partially explained by the fact that irreversible mechanical injury such as tearing and destruction of the nerve tissue and its vascular structures is the major CNS damage caused by *Gnathostoma* spp. (Boongird et al., 1977).

12.3.5. Geographical distribution and epidemiology

Human gnathostomiasis mainly occurs in Southeast Asia, P.R. China, Japan, India, Mexico and Ecuador (Herman and Chiodini, 2009). The highest number of human cases are found in Japan, Thailand, Vietnam and Mexico, from where hundreds of infections are reported every year (Ogata et al., 1998; PAHO, 2003; Rojekittikhun, 2002a). In Japan, a total of 3225 cases were documented between 1911 and 2001, with a peak in the period 1941–1965 (Ando, 2005). No specific figures on human gnathostomiasis in Thailand are available, but the number of cases documented in some hospital-based surveys indicates the relatively common character of this parasite. Overall 528 patients were clinically diagnosed with gnathostomiasis in Siriraj Medical School Hospital during the period 1940–1945 (Rojekittikhun, 2005). Approximately 900 cases were diagnosed in Thailand in 1961, 1962 and 1963 (Rojekittikhun, 2002a). Annually, 300–600 gnathostomiasis patients were admitted to the Hospital for Tropical Diseases affiliated to Mahidol University during 1985–1988, and 100–400 new suspected cases were admitted to the same hospital yearly, starting in 1989 (Rojekittikhun, 2002a). Approximately 60 cases have been reported from the mainland of P.R. China. Since the parasite is highly prevalent among animals, it is conceivable that gnathostomiasis is underestimated in P.R. China, which can be attributed to the unavailability of immunological tests, as well as lack of awareness among clinicians.

The cutaneous form is predominant in human gnathostomiasis and CNS involvement is a rare entity. However, considerable numbers of NG have been found in Thailand. During a 3-year clinical observation in the mid-1960s, 162 patients were presumptively diagnosed with NG (Punyagupta et al., 1990). Similarly, a 5-year study in the early 1970s identified 24 patients with eosinophilic meningitis or radiculomyelitis probably caused by *G. spinigerum* (Boongird et al., 1977). Another 39 cases were reported from the same hospital during 1980–1985 (Schmutzhard et al., 1988). Interestingly, few cases of NG were reported outside Thailand. The following points are offered for consideration. First, thousands of gnathostomiasis cases have been identified in Thailand and

thus the number of NG cases should far exceed those in other countries, despite the low frequency of CNS involvement. Second, *G. spinigerum* is the most common species responsible for human cases in Thailand. Compared to other species, *G. spinigerum* tends to migrate deeper into the skin and thus arguably has a higher chance of entering the spinal cord and brain (Ando, 2005; Rojekittikhun, 2005).

Gnathostoma is widely distributed throughout Southeast Asia and the Far East, but the locally predominant species differ between areas. Clearly, *G. spinigerum* is the most common species: about 51.7% of 120 parasitologically diagnosed patients were attributed to *G. spinigerum* in Japan, and all 20 patients from whom adult worms were recovered were parasitised by this species (Ando, 2005). In P.R. China, *G. spinigerum* accounts for approximately 95% of all reported cases. In Thailand, *G. spinigerum* is considered the only cause of human gnathostomiasis although five species have been documented in the country (Rojekittikhun, 2002a). *G. hispidum* and *G. doloresi* are mainly found in Japan and P.R. China. *G. nipponicum* is endemic in Japan. Another species, *G. malaysiae* is the suspected cause of human gnathostomiasis in Malaysia.

The life cycle of *Gnathostoma* spp. can involve numerous animals as intermediate and paratenic hosts, which complicates the route of human infection. In Thailand, for example, 48 vertebrate species were found naturally infected with L_3 of *G. spinigerum* (Rojekittikhun, 2005). Investigations of freshwater fish sold on markets in Thailand, Vietnam and Myanmar showed high *G. spinigerum* infection rates and intensities (Chai et al., 2003; Le and Rojekittikhun, 2000; Rojekittikhun et al., 2002, 2004; Saksirisampant et al., 2002; Sieu et al., 2009; Sugaroon and Wiwanitkit, 2003). Swamp eels (*Monopterus albus*) were identified as the most important host. Studies showed that the infection rate of swamp eels from Thai markets ranged from 10.7% to 44.1% (Rojekittikhun et al., 2002, 2004; Saksirisampant et al., 2002). The highest worm burden observed in one fish was 2583. In southern provinces of Vietnam, the monthly prevalence in swamp eels varied between 0.8% and 19.6% (Sieu et al., 2009). The highest incidence in Southeast Asian countries is associated with the rainy season (Le and Rojekittikhun, 2000; Maleewong et al., 1992; Sieu et al., 2009; Wiwanitkit, 2004). Snakehead fish is the leading source of infection in Japan where 603 cases were attributed to the consumption of this fish (Ando, 2005).

The exponential growth of aquaculture (Keiser and Utzinger, 2005) and the increasing share of freshwater fish produced in local aquaculture ponds across Eastern Asia places many people at risk of gnathostomiasis. The low host specificity means that humans can acquire the infection through a variety of food items, and increasing travelling puts individuals from non-endemic areas at risk of infection (Moore et al., 2003). The percentage of travellers infected with *Gnathostoma* spp. from non-endemic

areas is growing (Gorgolas et al., 2003). Embracing local cultural habits, which includes consumption of local delicacies, has become an important trait for many travellers (Herman and Chiodini, 2009). It is therefore not surprising that outbreaks have occurred among non-native populations. Indeed, cases of human gnathostomiasis have been observed among Koreans living in Myanmar (Chai et al., 2003), although few local cases had been reported previously.

It should also be noted that the prevalence of *G. spinigerum* has declined in some regions. In Japan, for example, the prevalence dramatically decreased in the 1970s, and neither larvae nor adult worms from animals have been reported since 1980 (Ando, 2005). On the other hand, more and more gnathostomiasis cases involving other species were reported. Since 1979, a total of 119 human cases caused by *G. hispidum* have been found in Japan, with 75.6% being attributed to loaches imported from P.R. China (Ando, 2005). *G. nipponicum* is only endemic in Japan and, by 2005, a total of 26 human cases had been reported (Ando, 2005). *G. doloresi* has been found in humans only in southern Japan from where 45 cases have been reported (Ando, 2005). Additionally, *G. malaysiae* was found in a Japanese man who consumed raw freshwater shrimps in Myanmar (Nomura et al., 2000).

12.4. CYSTICERCOSIS

A detailed account of the epidemiology and control of *T. solium* cysticercosis/taeniasis is provided elsewhere in volume 72 of the *Advances in Parasitology* (Willingham et al., 2010). Hence, an attempt has been made here to shorten this contribution to a minimum to avoid excessive overlap.

12.4.1. Pathogen

Cysticercosis is caused by cysticerci (larvae) of the swine tapeworm *T. solium*. Cattle and swine tapeworms are among the few helminths already described in ancient times (Del Brutto et al., 1998). Symptoms due to the presence of adult worms in the human small intestine are usually mild, but cysticercosis is a serious disease, recognised in the report of a human case more than 400 years ago (Del Brutto et al., 1998). Differentiation of *T. solium* and *T. saginata* was accomplished in the middle of the nineteenth century (Grove, 1990). The public health importance of NC was emphasised by British scientists in the 1930s, who recognised the disease among soldiers returning from India (Wadia and Singh, 2002).

The life cycle of *T. solium* includes two hosts: humans are the only natural definitive host and pigs act as intermediate host. The adult worms parasitised the upper small intestine of humans and the gravid segments

with the eggs are excreted in faeces. When ingested by pigs, the eggs hatch and oncospheres are liberated in their intestine. Oncospheres enter the bloodstream through the intestinal wall, settle in different organs and tissues and develop into cystic larvae (cysticercus). Cysts containing viable larvae are found mainly in skeletal muscles, subcutaneous tissue, eyes and the CNS (Graeff-Teixeira et al., 2009). The cysts reach their maximum size (~1 cm) within 2–3 months and seldom trigger obvious perilesional inflammation (García and Del Brutto, 2005). Upon ingestion by humans, live cysticerci develop into adult worms within 5–12 weeks (Muller, 2002).

Humans can also serve as accidental intermediate hosts for the parasite if *T. solium* eggs are ingested. The oncospheres penetrate the intestinal walls and are dispersed via the bloodstream throughout the human body. They develop into cysticerci but then usually die, followed by calcification. In immunologically privileged sites such as the CNS and the eyes (García and Del Brutto, 2005), cysticerci remain viable for several years and induce few inflammatory reactions in the surrounding tissues (Carpio, 2002). A lack of adequate sanitation and hygiene behaviour are considered key risk factors for environmental contamination with *T. solium* eggs, and hence drivers for human cysticercosis (García and Del Brutto, 2005). Recent epidemiological studies demonstrate clustering of NC patients around tapeworm carriers (Lescano et al., 2009; Sarti et al., 1994), suggesting direct human-to-human transmission. External and internal autoinfection has also been suggested; 5–50% of all *T. solium* carriers develop cysticercosis (Carpio, 2002) and a high taeniasis prevalence is found among patients with NC (Gilman et al., 2000).

12.4.2. Clinical manifestations

The typical neurological symptoms of NC result from cystic degeneration after a variable but often long incubation period (Carpio, 2002). Although the latent period of NC is difficult to determine, a study among British soldiers returning from India provided an estimate of several years (Mac Arthur, 1934). Symptomatic NC results from a combination of factors, including the amount, stage and location of cysticerci in the nervous system and the host's immune response (García and Del Brutto, 2005). NC can induce virtually any neurological symptoms but seizures (epilepsy) and symptoms related to intracranial hypertension are most commonly found (Del Brutto et al., 1992; Scharf, 1988; Sotelo et al., 1985). Seizures occur in 52–75% of all NC patients admitted to hospital (Guo et al., 2001; Sotelo et al., 1985; Wei et al., 1988; Zhang and Li, 1999), with higher rates among children (Sáenz et al., 2006; Singhi et al., 2000). NC has been recognised as a leading cause of acquired epilepsy (Senanayake and Roman, 1993). Generalised seizures or partial seizures with secondary

generalisation are common in adults (Carpio, 2002; Del Brutto et al., 1992; Sotelo et al., 1985), while paediatric cases tend to present with partial seizures (Gogia et al., 2003; Murthy and Yangala, 2000; Ruiz-García et al., 1997; Singhi and Singhi, 2009; Singhi et al., 2000). Seizures generally occur in the degenerative phase of cysticerci due to an inflammatory reaction or in the calcification phase due to perilesional oedema, and can be accompanied by other neurologic symptoms. Most symptoms apart from seizures are transient or mild. For example, in a clinical observation of 1400 cases, 46.1% reported seizures as the initial symptom and 40.1% had seizures with no other symptoms observed (Wei et al., 1988).

Headache is commonly reported, probably as a result of increased intracranial pressure and meningitis. Intracranial hypertension usually causes more severe headache, whereas meningitis often results in moderate headache (Guo et al., 2001). Hydrocephalus secondary to chronic meningitis or ventricular cysticercosis is the main cause of intracranial hypertension (Sotelo et al., 1985; Wei et al., 1988), triggering headache, vomiting, diplopia, papilloedema and even intracranial herniation resulting in death. Compared to adult patients, a lower incidence of headache and intracranial hypertension is seen in children but seizures are more common (Sáenz et al., 2006); 18–32% of all paediatric cases reported headache and 15–32% mentioned vomiting/nausea (Gogia et al., 2003; Rosenfeld et al., 1996; Ruiz-García et al., 1997; Singhi et al., 2000). Less common symptoms in children include cranial nerve palsy, motor neurodeficit, papilloedema, altered mental status, learning disability and behavioural disturbance.

Epidemiological surveys suggest that only a small fraction of the infected population shows symptoms (Diaz et al., 1992; Fleury et al., 2003, 2006; Sanchez et al., 1999). The introduction of neuroimaging techniques such as CT and MRI has revealed a wide spectrum from mild infections in asymptomatic individuals and patients with sporadic seizures to heavy infection and high morbidity, thus changing the perception of NC from a fatal or severe disease to a more variable one (García and Del Brutto, 2005). Recently, several population-based surveys in hyperendemic areas showed that 7–9% of all asymptomatic residents presented one or several calcified intraparenchymal brain lesions in CT scanning (Fleury et al., 2003, 2006). Most asymptomatic cases identified by CT scan had single calcified lesions compatible with NC, probably due to low infection intensity and rapid death of the cysticercus caused by the host's immune system (García and Del Brutto, 2005).

12.4.3. Diagnosis

In the absence of highly sensitive and specific diagnostic assays, a set of diagnostic criteria for NC has been proposed, including epidemiological risk factors, typical symptoms, neuroimaging results and serological tests,

as well as the results of trial therapy (Del Brutto et al., 2001). Living in, or frequent travel to endemic areas, is an important risk factor. Consumption of certain dishes, such as chicharrones in Latin America and pork lawar in Southeast Asia are risk factors for the disease (Fang, 2002; García et al., 1998; Ito et al., 2005). Although up to 50% of all seizures in developing countries may be linked to NC, many other causes must be considered in differential diagnosis (Senanayake and Roman, 1993). Non-invasive diagnostic techniques such as neuroimaging and immunoserological assays have greatly improved diagnosis (White, 2000). The images of lesions vary depending on the larval stages and examination techniques. MRI is more accurate than CT, but the latter is more widely available in low-income countries. The typical image of a viable cyst presents as a ''hole-with-dot'', with the scolex as a bright nodule within the cyst (Del Brutto et al., 2001). Degenerating cysts appear as contrast-enhancing rings or nodules surrounded by areas of brain oedema (García and Del Brutto, 2005). At this stage, the scolex is not usually seen but improved imaging techniques such as diffusion-weighted MRI may still visualise the scolex in degenerating cysts (García and Del Brutto, 2005). Calcified cysts appear as punctate hyperintense dots in CT scans, or as areas of subtracted signal in MRI visualizations.

A host of serological assays to detect specific antibodies have been developed. Recently, an enzyme-linked immunoelectrotransfer blot (EITB) with purified glycoprotein antigens has been confirmed to be sensitive if used on serum samples or CSF (Tsang et al., 1989; Wilson et al., 1991). An advantage of EITB is that its sensitivity in serum samples is equal to or higher than that in CSF samples (García et al., 1991). Although the reported specificity and sensitivity of EITB are 100% and 98%, a shortcoming is that ~30% of the patients with a single brain cysticercus may test negative (Prabhakaran et al., 2004). Serological assays may also fail to detect calcified cysts (Fleury et al., 2003; Schantz et al., 1994).

12.4.4. Treatment and clinical management

The treatment of NC is complicated by the evolving stage and location of the parasite. Interventions include anthelminthic drugs, anti-inflammatory drugs, antiepileptic drugs (AEDs) and surgery (Nash et al., 2006). Praziquantel and albendazole are most commonly used in the treatment of NC (Nash et al., 2006). Praziquantel shows satisfactory efficacy and is well tolerated at a dose of 50 mg/kg/day for 15 days (García et al., 2002). Regimens with variable doses and duration have also proven efficacious (Bittencourt et al., 1990). Albendazole was initially recommended at a dose of 15 mg/kg/day for 1 month (Sotelo et al., 1990). Subsequent studies showed that at the same doses, the treatment duration could be

shortened to 1 week or even 3 days without compromising on efficacy (Del Brutto et al., 1992; Sotelo et al., 1988). A comparison between praziquantel and albendazole produced conflicting results, but albendazole appeared to be generally more efficacious than praziquantel (Sotelo et al., 1990). Current evidence favours anthelminthic therapy in patients with viable or degenerating cysts in the brain parenchyma or in the subarachnoidal space at the convexity of the cerebral hemispheres (Del Brutto et al., 2006). Thus far, the role of anthelminthic drugs in the management of ventricular cysts has not been adequately studied.

Corticosteroids as an anti-inflammatory agent are recommended in the treatment of active NC manifesting as encephalitis, angiitis or chronic meningitis, and if subarachnoidal cysts are present. Antiseizure treatment including AEDs is important for all epileptic patients (Nash et al., 2006), in addition to antiparasitic therapy which apparently also plays a role in reducing the frequency of seizures (Del Brutto et al., 1992; García et al., 2004). Many patients remain seizure-free while under AED treatment, but suffer relapses after drug discontinuation, indicating that the intracranial cysticerci are permanent substrates for seizures and may be re-activated when the inhibitory influence of AEDs is withdrawn (Nash et al., 2004). Prognostic factors associated with seizure recurrence include the development of parenchymal brain calcifications, and the presence of recurrent seizures and multiple brain cysts before the onset of therapy (Del Brutto, 1994).

Surgical treatment of NC has lost prominence, especially since the advent of efficacious, safe and inexpensive anthelminthic drugs. However, it still plays an important role in relieving acute intracranial hypertension secondary to ventricular cysticerci or single huge cysts (Colli et al., 1986). Shunt dysfunction is the main problem in these cases and thus shunt placement and cyst removal are the main interventions. However, shunt failure rates are high and secondary meningitis may occur (Colli et al., 1986, 2002). It was suggested that the failure rate might be lowered through concurrent administration of antiparasitic drugs or steroids (Del Brutto and Sotelo, 1990; Martinez et al., 1995; Suastegui Roman et al., 1996). Recently, less invasive procedures such as endoscopic resection have been used to remove ventricular cysts (Bergsneider, 1999; Cudlip et al., 1998; Neal, 1995), resulting in less sequelae than open surgery (Bergsneider et al., 2000).

12.4.5. Geographical distribution and epidemiology

T. solium infections including taeniasis and cysticercosis are a global public health problem. Highly endemic areas are located in Latin America, Asia (mainly P.R. China and India) and sub-Saharan Africa (Carpio, 2002). Cysticercosis is a common zoonotic infection in P.R. China where

T. solium infections have been reported from 29 provinces (Xu et al., 1999b). Most cases are clustered in the northeast (Heilongjiang, Jilin and Liaoning provinces), centre (Henan, Hebei and Shandong provinces) and southwest (Yunnan province and Guangxi Zhuang autonomous region) of the country. A systematic review suggests that the average prevalence of *T. solium* infection was 0.11% (range: 0.05–15%) in endemic areas, with an estimated total number of *T. solium* carriers of 1.26 million (Chen et al., 2004). The prevalence of cysticercosis ranged from 0.14% to 3.2% and the estimated number of cysticercosis cases was 3–6 millions (Chen et al., 2004). The second national survey on important human parasitic diseases carried out in P.R. China, between 2001 and 2004 indicated that the seroprevalence was 0.55% across all tested populations (Wang, 2008). Seropositives were found in 25 out of 31 provinces covered in this survey. A retrospective survey in the hospitals of 23 endemic provinces identified 11,196 cysticercosis inpatients during the period 1991–2001 (Wang, 2008). Yunnan, Hebei and Heilongjiang provinces accounted for 77.9% of all hospital cases, and NC was predominant with a prevalence of 91.0%.

Taeniasis and cysticercosis are moderately endemic in Southeast Asia (Carpio, 2002). In Indonesia, *T. solium* infections are limited to the non-Muslim population in north Sumatra, Bali and Irian Jaya (Simanjuntak et al., 1997). Up to 51% of all Christians and animists in some localities of Irian Jaya harboured *T. solium* (Margono et al., 2003). A recent community-based study on cysticercosis showed that 2.2% of the study participants had been exposed to *T. solium* in Malaysia (Noor Azian et al., 2006). Human cysticercosis is also endemic in northern Vietnam where 100–150 patients are admitted to specialised hospitals every year (Dorny et al., 2004). The seroprevalence of cysticercosis is less than 6% (Dorny et al., 2004; Erhart et al., 2002; Somers et al., 2006). About 0.2–7.2% of the residents harboured tapeworms (Willingham et al., 2003). In Thailand, the prevalence of taeniasis is lower than 1%, but in the north of the country, the prevalence can be as high as 5.9%. Since the mid-1960s, less than 500 cases were diagnosed in Thailand. Immunoserological assays revealed a higher prevalence of cysticercosis, but *T. saginata* was the dominant *Taenia* species in the country (Waikagul et al., 2006). In Lao People's Democratic Republic (Lao PDR), several surveys conducted over the past 20 years found a prevalence of human taeniasis ranging from 0% to 14.0% (Conlan et al., 2008). Few data regarding *T. solium* infection in human populations are available from Cambodia and Myanmar.

Human cysticercosis has been identified as an eradicable parasitic disease, but current global efforts are unsatisfactory, and hence control, let alone local elimination and eradication, will be difficult to achieve in the near future (Pawlowski et al., 2005). In P.R. China, *T. solium* infection was listed as a national priority for control as early as 1956 (Xu et al., 1999a). Nationwide control programmes, including stricter meat

inspection and improving sanitary conditions, were implemented in the following decades. Today, 200,000 tons of pork meat are rejected each year due to cysticerci, an annual loss of 1 billion Chinese Yuan (about US$ 121 million) (Ito et al., 2003). However, the situation in many rural areas has not markedly changed with pigs raised and slaughtered under traditional husbandry practices. This is especially true in remote areas with little transportation infrastructure (Steinmann et al., 2007). Consumption of raw pork is closely associated with the endemicity of *T. solium*. For example, up to 80% of all raw pork bought on local markets was used to prepare the local favourite dish ''shengpi'' of thin-sliced raw pork in some villages of Dali prefecture in P.R. China (Fang et al., 1995). In some rural areas of southwest P.R. China, latrines are uncommon and pigs roam freely (Steinmann et al., 2008), conditions facilitating the transmission of *T. solium* between humans and pigs. In other areas, latrines are available but fresh human faeces are used to fertilize crops (''night soil'') (Willingham et al., 2003). Indeed, *Taenia* eggs have been recovered from a variety of vegetables and fruits available in local markets in endemic areas (Kozan et al., 2005). Thus, improving sanitary conditions, pig husbandry practices, meat inspection and health education is considered decisive for breaking the transmission cycle and to render cysticercosis control sustainable.

12.5. SPARGANOSIS

12.5.1. Pathogen

Human sparganosis is caused by the sparganum of *Spirometra* spp. Human ocular sparganosis was described in the book ''Compendium of Medical Herbs'' as early as 1596. The first case of *Spirometra mansoni* was isolated as a sparganum from a man in P.R. China in 1882. The adult *Spirometra mansoni* was first described in 1929, when adult worms were successfully isolated from the intestines of experimentally infected animals (Faust et al., 1929). Six years later, Mueller discovered a similar species in Syracuse cats in the United States and temporarily named it *Diphyllobothrium mansonoides* (Mueller, 1935). Subsequent studies showed that this species was morphologically different from *Spirometra mansoni* and variations in its life history were noted, leading to the establishment of a new species, *Spirometra mansonoides* (Mueller, 1935, 1974). Their pathogenicities are similar and, today, they are considered to be responsible for most human sparganosis cases in Asia and the Americas, respectively (Holodniy et al., 1991). In 1918, Takeuchi reported the first case of neurosparganosis (NSP) (Takeuchi, 1918). It is estimated that 3.2% of all patients develop NSP (Wu, 2005).

The life cycle of *Spirometra* is complex and involves three hosts. Adult worms dwell in the intestine of carnivores such as cats and dogs. Their eggs are passed in the faeces and hatch in freshwater, releasing L_1, the coracidia. These larvae are consumed by *Cyclops* spp. (the first intermediate host), in which they develop into L_2, the procercoids. When infected *Cyclops* spp. are consumed by a second intermediate host such as frogs, the larvae penetrate the bowel wall of the new host and migrate to various organs and tissues where procercoids develop into spargana. A variety of paratenic hosts are known; many amphibians, reptiles and even mammals were found to be naturally infected with spargana. It proved difficult to identify their route of infection and both ingestion of *Cyclops* and preying on frogs have been proposed. Once the second intermediate host or paratenic host is consumed by a cat or dog, the spargana develop into adult tapeworms in their intestine within approximately 3 weeks. Adult worms then live for up to 3–4 years.

Humans can become accidental definitive hosts, second intermediate hosts or paratenic hosts. Adult worms parasitising the intestine of humans are rare and result in few health problems. However, spargana can invade any organs or tissues and thus are medically more significant. The migration route of spargana to the CNS is not known but a sparganum may accidentally migrate through the foramina of the skull base and vertebral column along the loose connective tissue surrounding vessels and nerves. Humans are infected in three main ways; firstly, by drinking water containing infected *Cyclops* spp.; secondly, by ingesting the flesh of second intermediate or paratenic hosts harbouring spargana, usually in the form of raw or undercooked meat; and thirdly, by applying the flesh or skin of infected intermediate hosts as a poultice to an open wound, whereby the sparganum can directly invade human tissues. Other transmission routes are rare. Ocular sparganosis may be attributable to direct contact with contaminated water (Leon et al., 1972) and trans-placental infection has also been hypothesised (Chen, 1983).

12.5.2. Clinical manifestations

The incubation period of NSP is variable but generally long. Two studies on NSP indicate an incubation period between 1 and 30 years (Kim et al., 1996; Song et al., 2007). However, estimating the incubation period is difficult since the exposure to the parasite can often not be identified. The incubation period of subcutaneous sparganosis is easier to determine because of the obvious migrating swellings. It is estimated to range between 1 day and several months (Chen et al., 2002; Huang, 2003; Lin et al., 2002).

Clinical manifestations of NSP depend on the regions involved. Seizures, hemiparesis and headache are the most common symptoms.

Approximately 84% of all patients with NSP experience a long history of seizures (Chang et al., 1992). The duration of symptoms is variable, ranging from 2 weeks to 24 years (median: 36 months) (Kim et al., 1996). Most patients present with generalised tonic convulsion, followed by motor weakness of the extremities. Long-term clinical manifestations often tend to be associated with generalised cognitive dysfunction and generalised degenerative changes in white matter, suggesting a chronic progressive inflammatory disease (Kim et al., 1996). Interestingly, NSP and subcutaneous swelling seldom occur simultaneously, which is probably linked with the observation that humans are usually infected by only one or a few spargana. Death is a rare outcome of NSP but can occur in the absence of appropriate treatment.

Involvement of the spinal cord is less frequent than cerebral manifestations. Symptoms depend on the location of the lesions; a typical clinical picture is back pain followed by progressive weakness of lower limbs (Fung et al., 1989; Kudesia et al., 1998; Liu, 2006; Wu et al., 1990). At an early stage, patients may experience repeated light fever for several months (Fung et al., 1989; Kudesia et al., 1998). Incontinence is not unusual in spinal sparganosis (Fung et al., 1989; Liu, 2006; Wu et al., 1990). At a later stage, patients may suffer from degeneration or loss of sensation such as pain and temperature in affected regions (Fung et al., 1989; Zhao et al., 1998).

12.5.3. Diagnosis

The definitive diagnosis of NSP is based on the discovery of a sparganum in the brain or spinal cord. In most cases, parasites are found during surgery or upon autopsy. Preoperative diagnosis of NSP can be made based on a combination of factors such as exposure history, clinical manifestations and findings from physical examination and laboratory tests. Although the exposure is complex, some specific behavioural traits are indicative (e.g. eating raw frogs, tadpoles and snakes or drinking snake bile and blood). These risk factors are present in some populations in the Far East and Southeast Asia, as is the practice of applying poultices made of frog flesh to open wounds.

There are no specific neurological symptoms indicative of NSP. Headaches, seizures, paraesthesia, hemiparesis and homonymous hemianopsia have been reported and depend upon the location of the worms as well as the amount of granulation tissue. Cytological examinations are usually normal. Eosinophilia is not always present in NSP, probably because most patients experience a long illness course and degenerated worms are enclosed by inflammatory granuloma. The neuroimaging findings are not specific but still provide important information. CT

characteristics of NSP include (i) unilateral involvement; (ii) extensive or multifocal areas of low density along white matter fascicles, with ipsilateral ventricular dilatation and localised cortical atrophy; (iii) nodular or irregular enhancement with spotty calcification; and (iv) change in the location of enhancing nodules on sequential scans (Chang et al., 1992). Recent studies showed that MRI (particularly contrast enhancement MRI) was superior to CT. The most important findings were the tunnel sign and multiple conglomerated ring or bead-shaped enhancements on MRI (Song et al., 2007).

Immunological assays for NSP have been developed and ELISA detecting sparganum-specific IgG antibodies have been widely used. Kim et al. (1984) reported the performance of serum ELISA for diagnosing individual patients. The study showed high sensitivity and specificity (100% and 95.7%, respectively), but there was cross-reactivity between *Spirometra* spp. and *Taenia* spp. Recent studies confirmed the value of immunological assays for diagnosis and showed that there was an agreement between serum- and CSF-derived antibodies (Chang et al., 1987; Kim et al., 1996; Song et al., 2007).

NSP is difficult to distinguish from brain tumours based on symptoms and neuroradiological findings. The majority of all patients are misdiagnosed as having a metastatic brain tumour (Fung et al., 1989). NSP should be considered whenever a patient has an unusual history incompatible with brain tumour, especially in sparganosis-endemic areas. Metastatic brain tumours often have a mass effect and compress the ventricle, while sparganosis seldom has a mass effect but is associated with adjacent ventricular dilation. Additionally, sparganosis shows the unique image of tunnel sign on post-contrast MRI (Song et al., 2007). Diagnosis can be complicated by larval migration (Eom and Kim, 2009; Kim et al., 2007) and the proliferative form (Lo et al., 1987).

12.5.4. Treatment and clinical management

To our knowledge, there is no treatment available against sparganosis and, thus far, no systematic evaluation of anthelminthic drugs has been performed. Anecdotal clinical data indicate that praziquantel was unable to kill live larvae or otherwise benefit patients who had not undergone surgery (Kim et al., 1996). Hence, surgery is the only option to improve the condition of patients with NSP. A prospective study showed that fair to excellent outcomes could be expected for patients from whom live worms or granuloma with degenerative worms had been completely removed. Improvement was only poor in patients who did not receive surgical removal and those in whom a granuloma with a degenerating worm had been incompletely removed (Kim et al., 1996).

12.5.5. Geographical distribution and epidemiology

Over 1400 human sparganosis cases have been reported from at least 39 countries (Qiu and Qiu, 2009), including imported cases related to international travel and migration. On a global scale, most cases are reported from the Far East, including P.R. China, Japan and the Republic of Korea (Korea) where *Spirometra mansoni* is endemic. Before 1998, 632 cases had been documented in P.R. China (Xu et al., 1999b), and over 100 cases were reported in the following years (Wu et al., 2007). Some 470 cases have been described in Japan (Kimura et al., 2003). A literature review documented 63 cases in Korea during the period 1917–1971 (Cho et al., 1975), and many sporadic cases have been reported thereafter. Southeast Asia is moderately endemic. Thirty-four cases have been described in Thailand (Wiwanitkit, 2005), and several cases have been reported from Indonesia, where the causative agent might be a species other than *Spirometra mansoni* (Margono et al., 2007). Only a few cases of sparganosis were reported from Vietnam, but case reports among Vietnamese emigrants and a deeply rooted tradition of eating frogs suggest the disease is endemic (Vortel et al., 1995).

NSP is uncommon; only five cases were identified among 34 sparganosis patients in Thailand (Wiwanitkit, 2005). Two out of 63 cases presented with spinal lesions in Korea (Cho et al., 1975). Less than 5% (18/542) of all cases in the mainland of P.R. China showed CNS involvement (Xu et al., 1999b). Recently, the number of reported CNS sparganosis increased in P.R. China (Wu et al., 2007), perhaps explained by advanced diagnostic tools that are more likely to reveal helminths in the CNS. Indeed, along with the wider application of non-invasive neuroimaging techniques such as CT and MRI, more accurate diagnosis of intracranial helminth infections has become possible (Song et al., 2007; White, 2000). However, a real increase in the number of NSP cannot be ruled out and might be associated with shifts in dietary habits and the involvement of new host species.

Consumption of frogs and snakes are recognised risk factors, but infections due to other animals may be under-diagnosed. *Spirometra mansoni* in pigs is not uncommon in P.R. China, with infections reported from at least 12 provinces (Wu, 2005). *Spirometra mansoni* is found in frogs from both tropical and temperate regions in P.R. China. The natural infection rate is variable, ranging from 3.2% to 100% (Qiu and Qiu, 2009), with an average sparganum burden of 2–7 per frog. Several frog species are important intermediate hosts, but the predominant species differs between locations. For example, *Rana nigromaculata* is the main host in western Guangdong province (Li et al., 2009), whereas *R. limnecha* is the predominant intermediate host in Fujian province (Wu and Lin, 2001). Frogs sold on local markets were also found to be infected. Recent investigations showed infection rates of 58.4–66.5% among frogs in markets in Guangzhou (Qi et al., 2008; Wu et al., 1997), 18.7% in Guiyang and 17.5%

in Ningbo (Wu et al., 2007; Ye et al., 2005). Snakes are an other important sources of infection. Since snakes prey on frogs, the infection rate among snakes is high. For instance, individuals of all seven snake species examined in a survey were infected by this parasite and the overall prevalence was 47.6% (Huang et al., 1990).

Social and economic development is impacting on risk factors, and hence the distribution of sparganosis. Enhanced access to clean water lowers the risk of infection, and consumption of raw tadpoles and frogs for medical purposes or applying frog flesh poultice to open wounds has lost in popularity with the availability of western medicine. However, in some rural and mountainous areas, beliefs prevail that frogs and tadpoles can treat some illnesses such as skin or oral ulcer, fever and open wounds (Qiu and Qiu, 2009). A recent clinical observation showed that all 13 sparganosis patients from Henan province in central P.R. China had acquired their infection by eating live tadpoles; the average number of tadpoles eaten by individual patients was 96 (range: 6–300) (Lin et al., 2008). Among them were 10 cases aged less than 12 years. A subsequent survey revealed that 36.6% (145/396) of the habitants of a single village had eaten live tadpoles as a local remedy to cure illnesses (Lin et al., 2008). A review of 378 human sparganosis cases in 1994 showed that 54.0% of the patients had applied frog flesh poultice (Zhao, 1994). The percentage dropped to 19.2% in 2007 (Wu et al., 2007). Contrasting with the use of frogs in traditional medicine, the consumption of frogs and snakes appears to be increasingly popular, although they are usually adequately cooked. A recent review showed that 34.6% of 104 sparganosis patients from P.R. China had a history of eating frogs or snakes (Wu et al., 2007). New risk factors have been described; consumption of raw snake blood and snake bile is increasingly popular in some areas and several cases of sparganosis were attributed to this behaviour (Lin et al., 2003a).

12.6. PARAGONIMIASIS

Comprehensive reviews pertaining to the epidemiology, clinical manifestations and control of food-borne trematodiases, including paragonimiasis, are available (Keiser and Utzinger, 2009; Sripa et al., 2010). Hence, the current section is kept as short as possible.

12.6.1. Pathogen

Pulmonary paragonimiasis is caused by adult *Paragonimus* worms, whereas cerebrospinal involvement can occur during worm migration. More than 50 species and subspecies of *Paragonimus* have been described (Blair et al., 1999), eight of which are major causes of human

paragonimiasis (Murrell and Fried, 2007). Five species, namely *P. westermani*, *P. heterotremus*, *P. miyazakii*, *P. ohirai* and *P. skrjabini*, are endemic in Southeast Asia and the Far East. The most important species is *P. westermani*. The first case of neuroparagonimiasis (NP) was described in 1887 after two adult worms were recovered from the brain of a patient (Oh, 1968a). The percentage of NP relative to the total number of paragonimiasis cases varies between different areas. In P.R. China, the percentage among hospitalised patients ranged from 9.8% to 19.7% (Zhao, 1994).

Details of the life cycle of *Paragonimus* spp. have been described elsewhere (Keiser and Utzinger, 2009; Sripa et al., 2010). In brief, adult worms live encapsulated in the lungs of mammals (e.g. humans, cats and dogs). The eggs are deposited into bronchial secretions and eliminated via sputum or swallowed and excreted in faeces. Miracidia are released after 2 weeks of embryonation once eggs have reached freshwater bodies. Larvae penetrate the first intermediate host snail (*Melania* spp.), and ultimately develop into cercariae. Crustaceans (e.g. crabs and crayfish) serve as second intermediate hosts, which become infected via direct penetration of cercariae or ingestion of infected mollusks. Cercariae then encyst and develop into metacercariae. Mammals acquire an infection through consumption of infected crustaceans that are not or insufficiently cooked. Metacercariae excyst in the small intestine and migrate through the intestinal wall to reach the abdominal cavity, enter the abdominal wall, and migrate to the pleural cavity. Typically, two maturing worms pair in the pleural cavity and move into the parenchyma of the lungs where a fibrous cyst develops and then mate and produce eggs.

Unlike in the case of angiostrongyliasis, gnathostomiasis, cysticercosis and sparganosis, humans are permissive definitive hosts for *Paragonimus* and worms migrate along a mostly defined route to their final destination, the lung. NP develops if worms accidentally migrate through the soft tissues along the vessels of the neck and via the jugular foramen into the CNS (Oh, 1968a).

12.6.2. Clinical manifestations

Pulmonary symptoms usually appear after an incubation period of at least 11 days and up to 6 weeks (Cui et al., 1998; Owatari et al., 1994). Cerebral involvement is not common in paragonimiasis and determining the incubation period of NP proved difficult, not least due to frequent exposure in endemic areas. A series of studies on paediatric patients indicates that the incubation period ranges from 1 month to 3 years (Cheng, 2004; Dai, 1997; Yin, 1997).

NP may present with a number of different symptoms, including eosinophilic meningitis, arachnoiditis, mass lesions, visual disturbances

and seizures. Most patients experience an insidious onset of symptoms, but a few suffer from acute meningitis (Li et al., 1996; Yin, 1997). About one-third of the NP patients report a history of meningitis, usually mild, transient and self-limiting (Oh, 1968a). The predominant manifestations are fever, headache and vomiting, as well as neck stiffness and Kernig's sign. The duration of meningitis is variable from 3 days to 15 weeks. Interestingly, 45% of patients with recurrent meningitis recovered spontaneously. Some patients may only present discrete headache (Li et al., 1996). Seizures are common and found in 16–87.8% of patients with NP (Cheng, 2004; Dai, 1997; Huang, 2000; Li et al., 1996). Other symptoms include visual disturbances, motor weakness and sensory disturbance. Ophthalmologic involvement was reported in three-quarters of these patients and hemiparesis, hemihypaesthesia and menigeal signs were also found. Another frequent finding is a worsened mental status. Specific disturbances include personality changes, a decline in intellectual function, disorientation and depressed consciousness. A declining mental status was seen in approximately 70% of all patients (Kusner and King, 1993).

The average incidence of spinal paragonimiasis in CNS infections ranges from 2.9% to 13.3% (Moon et al., 1964; Oh, 1968b, 1969). The typical clinical picture of spinal paragonimiasis is a long history of coughing and rusty sputum, followed by radicular pain. Subsequently, patients experience progressive motor weakness and sensory loss in the lower extremities and often urinary and faecal incontinence.

12.6.3. Diagnosis

NP patients show both neurological and pulmonary symptoms, with the former preceding the latter in one-third of the patients (Oh, 1968a). Thus, a history of pulmonary paragonimiasis (i.e. coughing and rusty sputum) is indicative for NP. Common symptoms such as seizures and progressive weakness in the extremities are additional useful indicators. While consumption of freshwater or land crabs and crayfish is common worldwide, specific risk factors such as eating ''drunk'' crabs and using crab juice are important for differential diagnosis at a local scale. The definitive diagnosis of paragonimiasis relies on the discovery of the worm during biopsy or its eggs in sputum or faeces. However, the diagnosis of NP is difficult since many patients do not present active pulmonary manifestations at the time of hospital admission (Higashi et al., 1971; Oh, 1968a). Eosinophilia in peripheral blood has limited value in the diagnosis of NP because only 43.8–62.5% of the patients present eosinophilia, mainly at the acute stage involving meningitis and in pulmonary paragonimiasis (Moon et al., 1964; Oh, 1968a). The eosinophil cell count in the CSF can be elevated when acute meningitis occurs, but it is usually unchanged in the case of

chronic meningitis or single spinal involvement (Higashi et al., 1971; Moon et al., 1964; Oh, 1968a,b).

Several immunologic assays and gene probes have been developed and are considered equivalent or even better than microscopic detection of parasite eggs (Maleewong, 1997). Today, imaging techniques play an important role for diagnosis. X-ray and more recently CT and MRI have been used, and findings of clustered ring-enhancing lesions, seen in approximately half of all early cerebral paragonimiasis cases, are suggestive of NP (Cha et al., 1994).

The diagnosis of NP is complicated by the presence of pulmonary changes due to tuberculosis (de Leon and Piad, 2005; Doanh et al., 2005) and NP can be confused with tuberculosis meningitis (Sharma, 2005). Distinguishing features are the acute onset and relatively mild nature of *Paragonimus* meningitis, compared to the gradual onset and more severe neurologic deficits seen in tuberculosis meningitis. Analysis of CSF shows an elevated cell count, increased pressure and elevated protein in 75% of the cases, and a depressed glucose level in 55%. Of note, in 80% of all NP patients, eosinophils constituted between 5% and 90% of the total CSF leukocytes.

12.6.4. Treatment and clinical management

Cerebrospinal involvement is rare and usually accompanied by pulmonary paragonimiasis. Although the mechanism of cerebrospinal involvement is unknown, treatment of pulmonary paragonimiasis should be an integral part of treating NP. Chemotherapy using praziquantel and triclabendazole has been recommended by WHO and is reviewed elsewhere in this thematic volume of the *Advances in Parasitology* (Keiser and Utzinger, 2010). In brief, recommended treatment regimens of praziquantel are either 25 mg/kg/day for 2 consecutive days or a single 40 mg/kg oral dose. Triclabendazole is recommended at a dose of 20 mg/kg/day in two divided doses given on 1 day. At present, triclabendazole is only registered in few countries, but efforts are underway by WHO to make the drug more widely available (Keiser and Utzinger, 2009). Bithionol had been widely used before praziquantel became available but cure rates are low-to-moderate (50–60%) and adverse events are common (Chen et al., 2001).

Surgical removal of the cysts or granulomas is the treatment of choice for NP, resulting in moderate to marked improvement (Moon et al., 1964). Treatment failure may occur if cysts and affected tissues are incompletely removed or diffuse atrophy of the cord is present (Higashi et al., 1971; Moon et al., 1964). Recurrence due to persisting *Paragonimus* infection has also been reported (Kusner and King, 1993). Thus, an integrated approach combining surgery and chemotherapy is indicated. Triclabendazole is

currently recommended for NP but praziquantel and bithionol had also been successfully used (Moon et al., 1964; Oh, 1968a). There is evidence indicating that therapy results in worsened symptoms due to the death of parasites and increased local inflammation. Therefore, corticosteroids may be required during treatment to decrease inflammation and oedema formation at the site of the lesion (Kusner and King, 1993).

12.6.5. Geographical distribution and epidemiology

Recent estimates put the number of people at risk of paragonimiasis at 293 million, and the number of infections at more than 20 million (Keiser and Utzinger, 2005, 2009). Approximately two-thirds of the infections are concentrated in P.R. China. A systematic literature review identified 23,703 cases in P.R. China before 1999, and a prevalence of 4.2% (452/10,692) for NP (Xu et al., 1999b). The recent national parasitological survey found a seroprevalence of 1.7% (Wang, 2008). In the 1950s, paragonimiasis was highly endemic in Japan; an extensive seroepidemiological survey indicated that the disease was endemic throughout the country with the exception of Hokkaido, the northernmost island. In subsequent decades, the seroprevalence steadily declined but the parasite has re-emerged in recent years (Nawa and Nakamura-Uchiyama, 2005). A similar situation is reported from Korea. It was estimated that more than 2 million people were infected in the late 1960s, as determined by intradermal tests, and about 40% of them were egg-positive (Cho et al., 1997). Along with socioeconomic development and environmental changes, the prevalence sharply declined in the 1990s. In recent years, approximately 100 cases were diagnosed annually by an ELISA test undertaken for clinical differentiation from tuberculosis.

Several studies have confirmed that paragonimiasis is endemic in at least seven provinces in northwest Vietnam (De et al., 2000; Doanh et al., 2005; Queuche et al., 1997; Vien et al., 1997). The prevalence among residents ranged from 0.2% to 15% (De et al., 2000; Doanh et al., 2005; Queuche et al., 1997). The egg-positive rate in sputum was as high as 28.4% among individuals reporting chronic coughing (Queuche et al., 1997). In Thailand, the prevalence of paragonimiasis has decreased over the past 2–3 decades. A recent study found that the egg-positive rate in sputum and stool declined from 6% and 1% in 1985 respectively to zero in 2005 (Yoonuan et al., 2008). However, the parasite infection among mountain crabs increased from 21.0% in 1985 to 35.9% in 2005 (Yoonuan et al., 2008). In the Philippines, the endemicity of paragonimiasis is currently unknown (de Leon and Piad, 2005). Previous studies showed that the parasite is endemic in the south of the country; eggs of *P. westermani* were frequently detected in sputum samples of ''tuberculosis'' patients, especially among ''drug resistant'' cases. Between 11.6% and 45% of all

tuberculosis patients or residents with chronic cough excreted *Paragonimus* eggs (Belizario et al., 1997; de Leon and Piad, 2005).

NP accounts for a small fraction of all *Paragonimus* infections. The recent national sampling survey in P.R. China identified 215 paragonimiasis cases from sampled hospitals among whom 24 showed CNS involvement (Wang, 2008). The percentage can reach 33.7% among hospitalised paragonimiasis cases in highly endemic areas; between 1979 and 1994, a total of 315 cases with paragonimiasis were found in three hospitals in Zhejiang province, and 106 patients suffered from CNS involvement (Li et al., 1996). A review of all 164 children hospitalised with paragonimiasis between 1975 and 1989 in a mountainous area of Hubei province found that 23.1% of them had developed NP (Zhang, 1990). In a similar study, 21.8% of 280 paediatric patients hospitalised between 1986 and 2006 suffered from CNS involvement (Li et al., 2008). In Vietnam, cerebrospinal involvement in human paragonimiasis occurred at a frequency of 1.3–8% (De et al., 2000; Queuche et al., 1997). Following the decline in *Paragonimus* infections, NP now is rare in Korea and Japan, while at the beginning of 1966 it had been estimated that about 5000 cases of NP existed in Korea (Oh, 1968a).

In P.R. China, *P. westermani* and *P. skrjabini* are the two most common pathogens causing paragonimiasis. Whilst *P. westermani* is the predominant species in the northeast and east of the country, *P. skrjabini* is endemic in the centre and south (Wu, 2005). The difference between *P. westermani* and *P. skrjabini* with regard to CNS involvement is not known, but it has been suggested that since the latter species usually migrates in subcutaneous tissue and viscera, it is more likely to involve the CNS (Wu, 2005). In Vietnam, at least four species have been found, but *P. heterotremus* was the most common one (Doanh et al., 2005, 2008). Although adult worms have never been isolated from patients thus far, human paragonimiasis in the country is assumed to be caused by *P. heterotremus*, since the morphology of the eggs in the sputum of some patients was suggestive of this species and metacercariae of this species are most frequently found in crabs commonly eaten in some areas (Doanh et al., 2005). In Thailand, six species have been identified in at least 23 provinces, but only *P. heterotremus* has been confirmed in humans (Waikagul and Yoonuan, 2005). In the Philippines, *P. westermani* is the predominant species (de Leon and Piad, 2005).

The prevalence of paragonimiasis is generally declining in the Far East and Southeast Asia. However, several factors potentially complicate the current situation. First, international travel, population movement and trade were linked to case reports outside traditional endemic areas. This is particularly obvious in P.R. China where many infections are diagnosed in non-endemic areas among migrant labour communities. An outbreak due to the consumption of raw crabs imported from Korea affected more

than 600 individuals in a Chinese border city (Kang et al., 2002). Second, additional paratenic animals are recognised as a source of infection. For example, paragonimiasis is re-emerging in Japan due to the consumption of raw wild boar meat (Uchiyama et al., 1999). Traditional eating habits are difficult to change. Barbecued crabs are believed to be an important source of infection for children in rural areas, especially in Vietnam and P.R. China (Doanh et al., 2005). Dishes such as drunk crab (P.R. China), soybean sauce-soaked crabs (Korea and P.R. China) and crab juice (Japan and Vietnam) are common routes of infection for adults. Health education targeting eating habits plays an important role in the control of this infection but struggles to succeed wherever people are accustomed to these dishes. Environmental change has been highlighted as an alternative way to decrease the prevalence of paragonimiasis. Many surveys documented a decline in intermediate host densities and in their prevalence of infection (Cho et al., 1997; Xu and Mao, 2002).

12.7. SCHISTOSOMIASIS

12.7.1. Pathogen

Human schistosomiasis is caused by five different *Schistosoma* species, namely *S. haematobium*, *S. intercalatum*, *S. japonicum*, *S. mansoni* and *S. mekongi*. The two species that are endemic in Southeast Asia and the Far East are *S. japonicum* and *S. mekongi*. Detailed reviews are available elsewhere in this thematic volume of the *Advances in Parasitology* (Muth et al., 2010; Zhou et al., 2010). In brief, *S. japonicum* in P.R. China has a documented history of over two millennia. The first parasitologically diagnosed case was described in 1888 in Japan (Grove, 1990). *S. mekongi*, previously considered an *S. japonicum*-like parasite, was first described in 1957 and firmly established in 1978 (Grove, 1990). Neuroschistosomiasis (NS) occurs when eggs end up in the CNS. The first report of NS was provided in an autopsy report by Yamagiwa in 1889 (Mitsuno, 1955). Approximately 2% of all patients with acute schistosomiasis japonica have CNS complications (Jaureguiberry and Caumes, 2008), but a higher percentage is observed in chronic and advanced stages with portal hypertension (Liu, 1993; Pittella, 1997). Only few NS cases due to *S. mekongi* have been reported (Carmody et al., 2008; Houston et al., 2004).

For a detailed description of the life cycle of *S. japonicum* and *S. mekongi*, the reader is referred to recent reviews (Ross et al., 2002; Utzinger et al., 2005; Zhou et al., 2010). In brief, male and female schistosomes pair, with the male holding the longer and thinner female in its body groove, and live in the mesenteric venous plexus of humans and mammals. Eggs must cross the intestinal wall and 25–30% of all eggs are

excreted in faeces while the others are trapped in the intestinal and vesical walls or carried to the liver and other organs via the portal circulation (Pittella, 1997). Larvae hatch when eggs reach freshwater bodies, releasing miracidia that penetrate the intermediate host snail, *Oncomelania* spp. for *S. japonicum* and *Neotricula aperta* for *S. mekongi*. Within 4–6 weeks, cercariae are released by the snail and actively seek a suitable definitive host (Gryseels et al., 2006). Immediately after skin penetration, the cercariae transform into schistosomula and reach the lungs via the circulation system. The schistosomula pass through the lungs and finally enter the portal system via the left heart. The adult worms pair and reach the mucosal branches of the inferior mesenteric and superior haemorrhoidal veins where the females start oviposition. The latent period in humans varies between 29 and 42 days for *S. japonicum* (Pittella, 1997).

Humans are permissive definitive hosts for both *S. japonicum* and *S. mekongi*. Eggs can accidentally end up in the CNS, but the route by which eggs enter the CNS is not clear. The most plausible route is via the retrograde abdominal venous flow to the veins of the spinal cord and brain through the valveless venous plexus of Batson (Liu, 1993). Alternatively, the eggs might enter the pulmonary or portal-pulmonary arteriovenous shunts in advanced hepatosplenic and cardiopulmonary schistosomiasis and then be carried to the CNS via the arterial system. Clusters of eggs in the brain parenchyma suggest that migration of adult worms to the spinal cord or cerebral veins followed by direct oviposition is another possible route, although adult worms have seldom been found in close proximity to the brain and spinal cord.

12.7.2. Clinical manifestations

The clinical manifestations of schistosomiasis vary depending on the developmental stage of the parasite. The typical signs and symptoms consistent with Katayama syndrome usually appear 2–12 weeks post-infection (Ross et al., 2007). The syndrome is characterised by non-specific signs and symptoms, such as fever, fatigue, myalgia, malaise, urticaria and non-productive cough. Eosinophilia in peripheral blood and patchy pulmonary infiltrates on chest radiographs are frequently detected. The symptoms of schistosomiasis japonica usually appear about 42 days after the first exposure or a re-infection or superinfection (Ross et al., 2001). The incubation period of neurological symptoms among a series of 42 patients with cerebral schistosomiasis japonica varied from 6 months to 9 years with an average of 2.3 years (Torres, 1965).

CNS involvement in schistosomiasis japonica can occur during or immediately after the acute phase of Katayama syndrome, or in an inapparent acute form without obvious systemic manifestations (Pittella, 1997). On the first occasion, usually accompanied by cerebral vasculitis

(Carod-Artal, 2008; Jaureguiberry and Caumes, 2008), the main neurological features are diffuse encephalitis and/or meningitis including headache, vomiting, speech disturbances, disorientation, visual abnormality, urinary incontinence, ataxia, motor deficit usually manifested as hemiplegia, hemiparesis or quadriplegia and even coma (Pittella, 1997). Some of these symptoms are transient and disappear within a few days or weeks. The tumoral form occurs more insidiously (Pittella, 1997). The resulting symptoms are related to increased intracranial pressure and a focal mass effect. Seizures accompanied by the loss of consciousness are the most frequently observed neurological symptoms in this form (Jing et al., 2007; Pittella, 1997). Additionally, headache, visual abnormality, sensory disturbance, papilloedema, hemiparesis and dysphasia are commonly observed (Jing et al., 2007).

The location of schistosome eggs in the CNS depends on the species. While the eggs of *S. japonicum* tend to accumulate in the brain, those of *S. mansoni* and *S. haematobium* usually reach the lower spinal cord (Liu, 1993). Therefore, the spinal form is relatively rare in Eastern Asia. Myelopathy includes granulomatous masses and transverse myelitis, which mainly involve the lower spinal cord (Jiang et al., 2008; Wan et al., 2006; Wang, 1984). The characteristic clinical picture is an initial burning pain radiating from the thoracolumbar region towards the lower extremities, followed by progressive weakness of the lower limbs, flaccid paraplegia, urinary incontinence, sphincter dysfunction and sensory disturbance from the pelvic girdle downwards. Schistosome myelitis has a similar spectrum of neurologic symptoms as those caused by granulomatous masses. It tends to result in a more acute systemic illness with a shorter incubation period than patients with schistosomal mass lesions. The onset is characterised by back or leg pain, followed by leg weakness or paralysis and sensory loss.

12.7.3. Diagnosis

The definitive diagnosis of NS relies on demonstrating schistosome eggs in granulomas in neural tissues. However, a preoperative diagnosis can often be established based on a set of criteria, but there is no single specific and sensitive indicator for NS. The appearance of typical neurological symptoms in patients who live in or travel to schistosomiasis-endemic areas should be considered as suspected NS cases. A diagnosis is then reached after ruling out other possibilities, especially other helminth infections and intracranial tumours. Clinical symptoms, immunological tests, imaging and laboratory findings should be considered in differential diagnosis. The clinical features of the tumoral form of NS are usually indistinguishable from those resulting from other slow-expanding intracranial lesions. Spinal cord NS, on the other hand, may be suspected

whenever 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). Clinical diagnosis is difficult whenever higher segments of the spinal cord are involved and if neurological symptoms progress slowly.

Eosinophil cells are often found in the blood or CSF, especially at an early stage. Steroid treatment strongly influences this indicator and eosinophil counts are usually normal if the patient was given anti-inflammatory drugs (Ferrari et al., 2004). The presence of eggs in the faeces is a suggestive finding. When faeces examination is repeatedly negative, rectal biopsy is recommended to boost sensitivity (Ferrari et al., 2004; Watt et al., 1986). The role of CT and MRI for diagnosing NS is still controversial. Imaging can show non-specific abnormalities in the CNS at a later stage or in seriously affected patients (Pittella, 1997). A recent study of cerebral schistosomiasis japonica showed multiple clustered, 1–3 mm sized enhanced nodules in the T1-weighted MRI (Liu et al., 2008). In spinal schistosomiasis, MRI may reveal an enlarged spinal cord (usually of the conus medullaris) with spotty enhancement after gadolinium injection, but atrophy may be demonstrated on CT and MRI several months after the initial signs (Pittella, 1997). Many immunoserological assays have been used to detect schistosome infections in patients with CNS involvement (Pammenter et al., 1991; Scrimgeour and Gajdusek, 1985), but none achieved sufficiently high levels of sensitivity and specificity. Monoclonal antibodies of various immunoglobulin isotypes have been tested for their ability to detect antibodies against soluble egg antigen of *S. mansoni* in CSF, and IgG1 were considered the most discriminating isotype marker for the diagnosis of NS (Ferrari et al., 1999; Magalhaes-Santos et al., 2003).

The extent of NS is probably underestimated since it is difficult to diagnose due to a lack of sensitive and specific diagnostic tools. It may be particularly neglected in patients with advanced schistosomiasis, often characterised by induced hydroperitoneum, since elevated intra-abdominal pressure increases the CNS invasion of eggs (Liu, 1993). In this case, the CNS involvement may be misdiagnosed as a secondary symptom of hepatosplenic and cardiopulmonary lesions. Diagnosis is especially challenging in patients without gastrointestinal symptoms and egg-negative stool examination (Zhou et al., 2009).

12.7.4. Treatment and clinical management

Comprehensive reviews are available for the treatment and community-based control of schistosomiasis (Chen, 2005; Utzinger and Keiser, 2004), and the discovery and development of antischistosomal drugs in P.R. China are reviewed elsewhere (Xiao et al., 2010). At present, praziquantel

is the only effective drug against all forms of schistosomiasis. It has only few and transient side effects and has been widely and effectively used in population-based control programmes, usually with a regimen of 40–60 mg/kg in single or divided doses (Chen, 2005; WHO, 2002). For the management of NS, a series of studies and clinical observations indicated good efficacy of praziquantel (Watt et al., 1986). It was observed that praziquantel tends to aggravate the condition at the early stage when steroid therapy is required (Jaureguiberry et al., 2007). Since other helminth infections in the CNS such as NC can be present simultaneously, a combination of praziquantel and steroids is recommended for all treatments of NS (Ferrari et al., 2008). The necessary duration of anti-inflammatory and anthelminthic treatment varies between individuals. Surgery to confirm the presence of schistosome eggs and granulomas is rarely used today. However, surgery is required for cases with medullary compression whenever chemotherapy is not successful (Jiang et al., 2008).

12.7.5. Geographical distribution and epidemiology

Schistosomiasis japonica is currently endemic in P.R. China, the Philippines and Indonesia. Schistosomiasis mekongi occurs in Lao PDR and Cambodia. For detailed information about the epidemiology of Asian schistosomiasis, the reader is referred to two accompanying reviews in this thematic issue of the *Advances in Parasitology* (Muth et al., 2010; Zhou et al., 2010). In brief, an estimated 726,000 people in seven provinces are infected with *S. japonicum* in P.R. China (Zhou et al., 2007). In the Philippines, an estimated 100,000 people are infected in three regions, namely Mindanao, Visayas and Luzon (Zhou et al., 2010). In Indonesia, less than 3000 people are infected in a few isolated villages. The total population at risk of schistosomiasis mekongi is estimated at 60,000 in Lao PDR and 80,000 in Cambodia (Urbani et al., 2002).

NS caused by *S. japonicum* occurs in about 2% of all patients with acute infections (Jaureguiberry and Caumes, 2008). The proportion can reach 4.3% among hospitalised adult schistosomiasis patients in P.R. China (Ross et al., 2001). Two cases with CNS involvement due to *S. mekongi* have been reported (Carmody et al., 2008; Houston et al., 2004). No population-representative data on NS exist, but data from single hospitals indicate that NS is a considerable problem in schistosomiasis-endemic areas. For example, 67 patients with NS were reported by the affiliated hospital of the Hunan Provincial Institute of Parasitic Diseases between 1994 and 2006 (Jing et al., 2007). Sixty-two cases were reported from a hospital in Jianli city in Hubei province between 2000 and 2004 (Liu et al., 2005). A retrospective survey covering 13 endemic counties in Anhui province documented 62 NS cases between 1997 and 2004 (Huang et al., 2008). No difference in risk factors for intestinal or CNS location of

schistosomes could be established; young male farmers and fishermen were at particular risk.

The number of NS cases is expected to decline in line with further progress made in the control of schistosomiasis. However, the advent of improved diagnostic techniques may increase the number of diagnosed cases. For example, wider availability of neuroimaging techniques such as CT and MRI facilitates an accurate diagnosis of NS. Some studies also indicated that NS caused by *S. mansoni* were associated with light infections and is primarily found in travellers from non-endemic areas as well as young immunologically naïve locals (Ferrari et al., 2008; Graeff-Teixeira et al., 2009). If the same situation were to exist for schistosomiasis japonica, the number of NS cases could be expected to increase as the prevalence further declines.

12.8. CONCLUDING REMARKS AND RESEARCH NEEDS

The major cerebrospinal helminthiases occurring in Southeast Asia and the Far East have been reviewed here, with key features summarised in Table 12.1. While NC is a well-known disease with a long history, other helminth infections involving the CNS are emerging, such as angiostrongyliasis. A general feature of helminthiases of the CNS is that their neurological manifestations are non-specific, and hence they are often missed or misdiagnosed in clinical practice. It is therefore recommended that a set of diagnostic criteria, including epidemiological history, clinical manifestations, results from physical examinations and laboratory findings were employed to improve diagnostic outcomes. The eosinophil cell count in the CSF or peripheral blood is an important indicator of helminth infection in general, but is often normal, especially in the chronic stages of infection. Neuroimaging techniques, including MRI and CT, have revolutionised the diagnosis of intracranial infections, although the images may not be specific. Immunological assays have been developed for many helminth infections, but their sensitivity and specificity are generally questionable. Chemotherapy proved effective for patient management but is still controversial for most infections. Anti-inflammatory drugs such as corticosteroids are often needed to suppress inflammation resulting from the degeneration of worms. Surgery is the treatment of last resort if chemotherapy is not available or ineffective and if patients present severe complications.

There are several important issues emerging in connection with helminth infections involving the CNS. First, the production and consumption of pork and aquatic products are rapidly increasing in Asia and put more people at risk of food-borne parasitic diseases such as cysticercosis, gnathostomiasis and paragonimiasis. The spread of exotic snail species

has contributed to the emergence of angiostrongyliasis in the mainland of P.R. China. Second, tourism and large population movements put people from non-endemic areas at risk. Third, the transportation and trade of food within and across countries may facilitate transmission beyond the known endemic areas. Fourth, other more traditional risk factors persist, e.g. special eating habits. For example, angiostrongyliasis is associated with the consumption of snails or slugs, sparganosis with that of frogs and snakes, or drinking snake bile and blood, and paragonimiasis with raw crab dishes. Although cysticercosis is not directly related to the consumption of raw pork, *Taenia* spp. infections may increase the risk of cysticercosis and help to sustain transmission.

Except for NC and angiostrongyliasis, cerebrospinal helminth infections are accidental. Reducing the overall prevalence of these parasites is therefore the most effective measure to control cerebrospinal helminthiases. For paragonimiasis, taeniasis and schistosomiasis, early treatment of infection is an important measure to prevent cerebrospinal involvement and other long-term sequelae. Health education and changing human behaviour is, in principle, effective to prevent all of these diseases, but is easier said than done. Food safety and hygiene is the basic issue for the control of food-borne diseases, whereas better access to clean water and adequate sanitation plays an important role for schistosomiasis prevention and control. Commercial farming in enclosed settings and using safe feed may be a way to guarantee food safety. However, its feasibility is questionable in low-income areas. Supervision and inspection are also required. Parallel to reducing the risk of infection, strengthening the awareness and diagnostic ability of clinicians plays an important role. Understanding the epidemic situation may be the first step to propose a robust control policy. Unfortunately, the cerebrospinal form of most helminthiases is frequently neglected or misdiagnosed, and hence the available data probably fail to reflect their real status. The establishment of rigorous surveillance systems focusing on combinations of symptoms rather than parasitological diagnoses alone and thus referring to a group of diseases sharing similar indicators is a measure of potential value.

Cerebrospinal helminth infections are a rare clinical entity, but an emerging public health issue. Several research priorities are highlighted here. First, effective diagnostic tools are needed. With regard to immunological assays against gnathostomiasis, for example, the immunoblot technique is now widely and effectively used for its diagnosis in Thailand (Rojekittikhun, 2005) and Japan (Ando, 2005). However, almost all gnathostomiasis cases in P.R. China are parasitologically diagnosed by biopsy, which is not feasible for cerebrospinal infections. The lack of immunological assays is an important explanation for the current underestimation of gnathostomiasis, and hence NG, in P.R. China. There is therefore a need to develop and validate immunological assays against

gnathostomiasis or to make existing ones readily available. Second, although mechanisms of CNS involvement are difficult to reveal, such information is necessary for enhanced patient management. For example, humans may take the place of the second intermediate hosts for *Gnathostoma* and *Spirometra* when they ingest infected copepods. Drinking untreated freshwater has been suggested as a route for human infection (Holodniy et al., 1991; Punyagupta et al., 1990), but whether the unusual role of humans increases the chance for parasites to enter the CNS is still a matter of debate. Third, concerted efforts are needed to evaluate existing anthelminthic drugs for the treatment of helminthiases affecting the CNS, including dose-finding studies and combination chemotherapy. For diseases where there is currently no effective drug available (e.g. sparganosis), there is an urgent need to develop such drugs. Although surgery can improve conditions of patients, infections with multiple worms call for chemotherapy. For existing drugs, a main problem affecting the evaluation of treatment efficacies for cerebrospinal helminth infections is the small number of potential participants. Collaboration among hospitals and disease outbreaks with sufficient numbers of people affected may provide opportunities to address this issue. Fourth, investigations on the burden of disease due to helminths invading the CNS are necessary. Indeed, neurohelminthiasis can result in epilepsy, paralysis, and hence loss of labour capacity. Surveillance networks on helminth infections of the CNS, facilitated by collaborations among different hospitals and disease control institutions in highly endemic regions, holds promise to reveal the true public health burden. Hospital-based surveillance systems potentially increase the capacity of detecting rare or neglected diseases, including neurohelminthiases.

Concluding, it is clear that helminth infections of the CNS in Southeast Asia and the Far East are an emerging public health problem, and concerted efforts are necessary to raise awareness of the public and clinicians to improve diagnosis and patient management. Special emphasis on the prevention of these infections through surveillance networks is needed, and decision-makers in the region are invited to engage actively in addressing this challenge.

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