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Update on Eosinophilic Meningoencephalitis and Its Clinical Relevance

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INTRODUCTION

The diagnosis of eosinophilic meningoencephalitis is based on clinical manifestations and microscopic identification of eosinophils present in cerebrospinal fluid (CSF). Routine CSF sediment examination and cell counts are usually done with fresh, unstained fluid samples, and eosinophils are difficult to identify in these preparations. This underdetection of eosinophils in CSF contributes to the underestimation of the prevalence of eosinophilic meningitis. Laboratory workers should be aware of the importance of correct differentiation of leukocytes in CSF with Giemsa or Wright stain. Although less than 2% of all meningitis cases have high CSF eosinophil counts (133), the presence of eosinophils is crucial for differential diagnosis and is thus extremely relevant.

The presence of eosinophils in the CSF should always be considered an abnormal finding. Some authors consider that CSF eosinophilia is defined by counts higher than 10 eosinophils per ml or 10% of the total CSF leukocyte count. These numbers most probably were arbitrarily chosen from studies of CSF cellularity in healthy individuals as cited by Kuberski (152) and have been accepted as the criteria for eosinophilic meningitis (230, 237, 295).

Helminthic infections are the most common cause of eosinophilic meningoencephalitis. Though less common, CSF-specific eosinophilia may also be associated with other types of infections, neoplastic diseases, drug use, prosthesis reactions, and miscellaneous idiopathic conditions.

The Eosinophils

Eosinophils participate in the inflammatory process of allergies, proliferative diseases, and helminth infections (1, 123). While neutrophils and macrophages destroy pathogens by endocytotic digestion, eosinophils are specialized in exocytotic degradation of large parasites, through the extrusion of cellular granules and contents. Together with mast cells, these leukocytes are present in small numbers as resident mucosal populations. These cell groups play a role in the surveillance for and response to foreign entities in the organism. Aside from their proinflammatory action, they also participate in regeneration and remodeling of tissues (1, 8). Eosinophilic inflammation is also associated with neoplastic proliferation of epithelial origin.

Eosinophils are considered important effector cells of the adaptive immune response. Specifically, they are involved in the Th2-type response, which is mediated by a complex array of cytokines (interleukins 2, 4, 5, 10, 12, 13, 16, and 18 and transforming growth factor), chemokines (RANTES and eotaxins), and lipid mediators (platelet-activating factor and leukotriene C4) (123). Antigen presentation, immune modulation, and inactivation of anaphylactic mediators are some of the active contributions of these cells to inflammatory responses (83, 110). Eosinophils can also contribute to tissue damage by a number of different mechanisms (146); e.g., loss of Purkinje cells and spongy changes in cerebellum white matter have been observed in experimental infection of mice with *Angiostrongylus cantonensis* (311).

Substantial in vitro data indicate that eosinophils actively destroy multicellular parasites, but in vivo data have been less conclusive (17, 146). In general, eosinophils preferentially destroy larval over adult worms (178). However, *A. cantonensis* appears to be an exception, as young adult worms of this species in nonpermissive hosts (mice and guinea pigs) are killed by CSF eosinophils (297). The ever-increasing evidence of complex and multiple actions of eosinophils and the variability associated with different hosts and parasite stages pose a challenge to clarifying the beneficial role of eosinophils in helminth infections (8, 146, 177, 186).

ANGIOSTRONGYLIASIS

The Parasite

The superfamily Metastrongyloidea includes cylindrical worms that live inside arterial vessels and cardiac cavities in a

FIG. 1. Female *A. cantonensis* worms are 22 to 34 mm long and show a dark red digestive organ, two white reproductive organs, and a transparent cuticle. (Courtesy of Juliano Romanzini, Grupo de Parasitologia Biomédica da PUCRS, Porto Alegre, Brazil; reproduced with permission.)

vertebrate host. These worms develop infective larvae during the intermediate mollusk stage. Due to the morphological heterogeneity of male bursa, Ubelaker (287) proposed grouping the species that have rodents as hosts within the genus *Parastrongylus*. This change in the name of the genus has not been widely accepted, though some have used *Parastrongylus* as a synonym for *Angiostrongylus*. Here we use *Angiostrongylus*, since a clinical awareness of angiostrongyliasis as a cause of eosinophilic meningitis has developed over the years.

A. cantonensis is the most important etiological agent of eosinophilic meningitis. The filiform male worms are 20 to 25 mm by 0.32 to 042 mm, and the females are 22 to 34 mm by 0.34 to 0.56 mm (Fig. 1). Another metastrongylid worm causing human disease is *Angiostrongylus costaricensis*. This parasite lives inside the mesenteric arterial system, can cause abdominal disease, and occurs throughout the Americas, from the southern United States to northern Argentina (198, 220).

History

A. cantonensis was first discovered in 1933, after examination of specimens recovered from both *Rattus norvegicus* (brown rats) and *Rattus rattus* (black rats) in Canton (now Guangzhou), China. Human infection was first reported in Taiwan in 1945, but it was not until the 1960s that cerebral angiostrongyliasis was recognized as an important public health problem. At that time, a parasite was recovered from a Filipino patient in Hawaii (241). Since then, two other *Angiostrongylus* species, *A. malaysiensis* in Southeast Asia and *A. mackerrase* in Australia, have been suspected but unconfirmed causes of neurological lesions in humans (64, 228).

Life Cycle and the CNS

A. cantonensis is a zoonotic parasite that affects rats as the primary hosts. Sexually mature male and female worms reside in the pulmonary arteries of rats, where the females lay their eggs. First-stage (L1) larvae hatch and migrate into rat feces via the trachea and the gastrointestinal tract. Mollusks are the intermediate hosts, in which the L1 larvae molt twice to produce the stage 3 (L3) larvae, which are infective for vertebrate animals. L3 larvae penetrate the vertebrate intestinal wall and migrate through the circulatory system. Over the course of 2 to 3 days, the larvae arrive at the brain. There, they molt twice and eventually develop into young adults inside meningeal vessels (Fig. 2). These young adults are carried to the pulmonary arteries and right heart cavities. Settlement in this final habitat occurs approximately 4 weeks after the initial intestinal penetration. In humans, L3 larvae molt twice and are hematogenously transported to the central nervous system (CNS), burrowing into neural tissue. The young worms do not complete their life cycle in humans and usually die, leading to intense inflammatory lesions (4, 172).

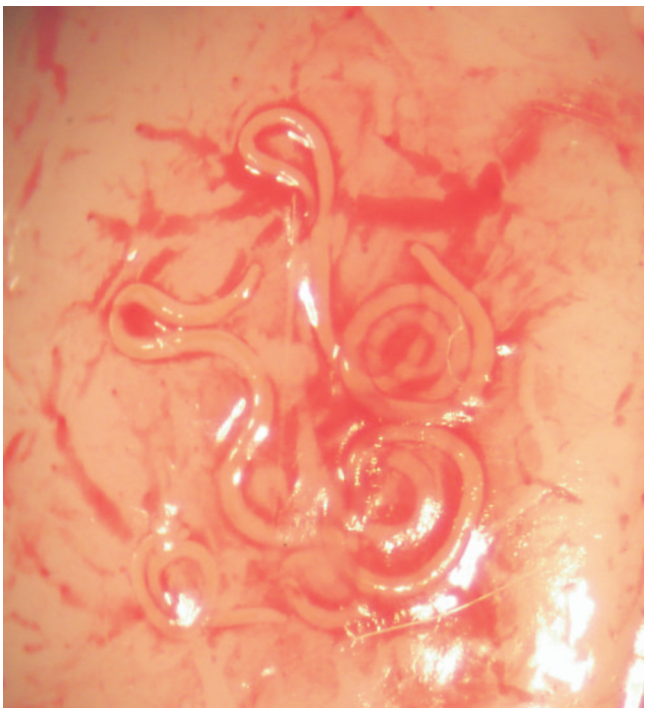

FIG. 2. Young *A. cantonensis* worms in brain tissue next to the meninges of experimentally infected *R. norvergicus*. (Courtesy of Camila Krug, Grupo de Parasitologia Biomédica da PUCRS, Porto Alegre, Brazil; reproduced with permission.)

Epidemiology

A. cantonensis has been found primarily in Asia, islands of the Pacific, and Australia but has also been observed in North, Central, and South America (2, 31, 33, 169, 293) and the islands of the Indian Ocean (e.g., La Reunion). The increasingly widespread travel of people has led to the detection of many imported cases of angiostrongyliasis and has become an important consideration in the differential diagnosis of neurological disease in travel medicine (3, 164, 262). Interestingly, although the parasite was originally described in China in the 1960s, it was not reported there again until 1984. Since 1984, several outbreaks have been detected in China, including a

severe cluster in Beijing of 160 cases (43, 171, 293). The outbreaks detected in Thai workers in Kaohsiung, Taiwan, and in U.S. travelers returning from a very brief stay in Jamaica highlight the importance of angiostrongyliasis as a risk for human health. In both situations exposure to infection probably took place at leisure time, either when individuals ate raw mollusks collected in ponds surrounding the factory in the case of the Thai workers or during a regular meal including a green salad in the case of the U.S. travelers (262, 281). With the exception of Taiwan, where most patients are children, *A. cantonensis* usually infects men in the third and fourth decades of life (127, 230).

The main mode of infection is the consumption of raw snails, reported by 51% in a study in Taiwan (127). Another source of infection can be other mollusks, and paratenic hosts, such as frogs, freshwater prawns, crabs, fish, and planaria. A less common path of infection is ingestion of contaminated vegetables, water, or fruit juice (262, 280). Hands may carry the larvae directly to the mouth, after manipulation of or playing with mollusks, which is likely the main mode of infection among young children. Like other parasites, whose larval stages develop inside mollusks, *A. cantonensis* is not specific to one intermediate host. Thus, many species of mollusks are susceptible to infection, though this may not carry great epidemiological importance. *Achatina fulica*, *Pila* spp., and *Ampullarium canaliculatus* are some of the main mollusk hosts in the *Angiostrongylus* life cycle. *Angiostrongylus* is a growing cause of concern in food safety, which has forced adjustments in protocols to ensure quality in both production and handling (233).

Disease

The presence of young adult *Angiostrongylus* organisms in the meninges and in the parenchyma of the medulla, pons, and cerebellum elicits an inflammatory reaction, known as eosinophilic meningoencephalitis. Careful study of these inflammatory sites has revealed a predominance of infiltrating eosinophils, with localized areas of suppurative necrosis and granulomatous reaction (137). The main initial complaint of infected patients is an acute severe headache (153, 281). This headache results from increased intracranial pressure produced by the widespread inflammatory reaction in the meninges.

Angiostrongyliasis is an acute disease that spontaneously resolves within in a few weeks, rarely entails sequelae, and is rarely fatal; the mean duration is 20 days, but it can range from 6 to 34 days (281). Early descriptions called it a "typical eosinophilic meningitis" (230), which distinguishes it from the more severe clinical picture of *Gnathostoma* meningoencephalitis. Typically, there is an acute severe headache with absent or low-grade fever, meningeal irritation, paresthesias, and occasionally paralysis of the cranial nerves (153, 230). The CSF is neither xanthochromic nor bloody, and there are no significant motor disturbances. Radicular pain, coma, and respiratory failure are all rare (251). Focal lesions do not indicate a clinical diagnosis of angiostrongyliasis. The vision may be affected directly by the presence of the worms in the eye or indirectly by cranial nerve paralysis leading to diplopia (127, 229). Table 1 lists the most prevalent clinical manifestations recorded in several clinical studies on cerebral angiostrongyliasis. A minority of patients manifest persisting paresthesias, weakness, and cognitive deficits, which may represent rare chronic forms of the disease (238). Clinicians should consider angiostrongyliasis when evaluating a patient with eosinophilic meningitis, even in regions outside its traditional geographic boundaries, especially when travelers or suspected imported food are involved (144, 262).

Diagnosis

Magnetic resonance imaging (MRI) examination of a patient with angiostrongyliasis often reveals multiple micronodular enhancements in brain tissues and linear enhancement in the pia mater. Complete resolution of abnormal MRI findings typically occurs after 4 to 8 weeks (127, 136, 281). Micronodules have also been detected in MRI imaging of lung parenchyma, which may reflect the presence of worms in that organ (136, 258).

Detection of young adults or L5 larvae is seldom possible, because few parasites probably enter the subarachnoid space, and a small volume of CSF is usually collected for examination. Larval recovery from the CSF was seen in 41.5% of 82 patients reported by Hwang and Chen in Taiwan (127). This impressive parasite recovery may be due to the larger amount of CSF that was collected with a pumping method (127). Overall, the detection of parasite count in CSF is consistently rare, as shown by the following incidence rates in a variety of reports: 2 out of 50 taps in 17 patients (281), 8 out of 125 patients (309), and 1 out of 54 patients (153). To date, no studies from Australia have reported detection of the parasite in CSF, although there was one necropsy that reported many worms in the subarachnoid space (228). Leaving the patient seated for a while prior to the collection of CSF by lumbar puncture is known to improve the chances of detecting worms (64, 281). The young adults are approximately 12 to 13 mm long. Table 2 lists references and websites with histological sections of *A. cantonensis* and other helminths causing eosinophilic meningoencephalitis.

Abnormal CSF protein and glucose are found in only a few angiostrongyliasis patients, and slight protein elevation is more common than glucose decreases (230, 281). In a group of patients described by Punyagupta and colleagues (230), only 32% showed normal protein levels, while 95% of patients showed normal glucose levels. Initial CSF eosinophil counts were below 10% in only 4% of the patients, but high counts were always consistent in second and subsequent examinations (230). Blood eosinophilia has been detected in up to 84% of patients at initial evaluation (127). Clinical presumptive diagnosis can be established by (i) clinical presentation with meningitis showing severe headache, (ii) a history of ingestion of raw mollusks, and (iii) prominent eosinophilia in the CSF.

Although intrathecal immunoglobulin measurements may help to improve diagnosis (84), differentiation among the helminthic causes of eosinophilic meningitis requires molecular diagnostic methods. Immunological methods of diagnosis have been under investigation since the early 1980s (65). Assays have been developed that either detect antibodies with purified antigens or detect antigens with monoclonal antibodies (Table 3). Reactivity to a 31-kDa component in Western blot (WB) analysis has been used for the evaluation of patients. At times,

TABLE 1. Frequency of clinical manifestations and evaluation of blood and CSF eosinophilia in four series of patients with cerebral angiostrongyliasis

Parameter	Result reported in reference:			
	281	230	127	154
No. (%) of patients				
Total	17	484	82	34
With symptom				
Headache	17 (100)	477 (99)	51 (62)	27/30 (90)
Neck stiffness	8 (47)	312 (64)		19/34 (56)
Fever	11 (65)	177 (37)	75 (91)	14/34 (41)
Paresthesia	2 (12)	181 (37)	2 (3)	14/26 (54)
Muscle weakness	8 (47)	4 (1)	19 (23)	
Orbital/retro-orbital pain	7 (41)		2 (3)	
Diplopia/blurred vision	2 (12)	184 (38)	10 (12)	3/34 (9)
Ataxia	1 (6)			
Nausea	4 (24)	186 (38)	18 (22)	
Vomiting	4 (24)	239 (49)	59 (72)	
Abdominal pain	3 (18)			
Aches: body and extremities		30 (6)		
Convulsions		17 (4)	16 (20)	
Facial paralysis		20 (4)	9 (11)	
Somnolence		30 (6)	17 (21)	
Urinary retention/incontinence		2 (1)	5 (6)	
With sign				
Stiff neck	11 (65)	72 (15)	65 (79)	
Brudzinsky's/Kernig's signs	11 (65)	27 (2)	26 (32)	
Hyperesthesia (pain)/paresthesia	3 (18)	20 (4)		
Impairment of vision	1 (6)	78 (16)		
Impairment of sensorium		26 (5)		
Facial palsy	1 (6)	21 (4)		
Mean incubation period (range), in days	13 (6–20)	17 (2–34)	13 (2–45)	NR[a] (2–18)
Eosinophilia				
% of patients with CSF prevalence (≥10%)	47	96	62	95
Avg initial no. in CSF (cells/mm^3)	100	700	NR	NR
% of patients with blood prevalence (criterion)	77 (≥10)	73 (≥10)	84 (≥10)	90 (≥3)
Avg initial no. in blood (cells/mm^3)	1,990	3,000	NR	NR

[a] NR, not reported.

the WB is preceded by a screening step with the less specific but highly sensitive enzyme-linked immunosorbent assay (ELISA) employing crude antigen (144, 226). Several serological tests based on ELISA methods have been used, although none are commercially available (88). This method requires *A. cantonensis* antigens prepared from larvae or young adults. Also, the detection of serum antibody has been found to be more sensitive than detection of CSF antibody (306). There is a great need for simple and less expensive procedures, such as the multi-immunoblot dot evaluated by Eamsobhana and colleagues (88, 89).

It is possible that antibody detection systems may not reveal early stages of infection. Studies of experimental infection in rabbits and mice have shown that the peak antibody response does not occur until 4 weeks after infection (167, 292). Among the antibodies detected, some may be derived from cross-reactions with other parasites (89, 92, 307). In this scenario, antigen detection methods such as ELISA-PCR may prove helpful (57) (Table 3). A method for detection of nucleic acids by real-time PCR has recently been applied to the diagnosis of two suspected cases in Brazil, but the method awaits further evaluation (A. C. A. Silva, unpublished data).

Treatment

Repeated spinal taps provide some therapeutic benefit, as they serve to decrease intracranial pressure. Both experimental infection studies and isolated reports indicate that killing the worms may exacerbate inflammation and increase the severity of the disease (164, 291). Prednisolone (60 mg/kg of body weight/day for 2 weeks) and albendazole (15 mg/kg twice a day [b.i.d.] for 2 weeks) were separately tested in the only two randomized placebo-controlled studies. Prednisone significantly reduced the proportion of patients with persistent headaches after completion of the treatment (9.1% compared to 45.5% in the placebo group; $P = 0.0004$), the mean duration of headache (5 days compared to 13 days; $P = 0.0$), and the number of repeated lumbar punctures for pain relief (7 compared to 22; $P = 0.02$) (52). The 2-week course of albendazole reduced the proportion of patients with persistent headaches from 20.6% to 40.6% in the placebo group ($P = 0.08$), and the mean duration of headache was reduced from 8.9 to 16.2 days ($P = 0.05$) (138). While a 2-week course of prednisolone (60 mg/day) may be recommended in meningitis caused by *A. cantonensis*, the value of albendazole or mebendazole therapy in conjunction with corticosteroids is not yet fully established,

TABLE 2. References and websites with images of histological sections from parasites causing eosinophilic meningoencephalitis

Agent or infection	Reference(s) and/or website
A. cantonensis	291 picasaweb.google.com/idintl/ParasitologyVolume2ForWeb02#5195514234701040466
Gnathostoma spp.	174, 120 www.fujita-hu.ac.jp/~tsutsumi/case/case190.htm
Schistosoma spp.	158 www.pucrs.br/fabio/atlas/parasitologia
Cysticercus	256 pro.corbis.com/images/42-18708066.jpg?size=67&uid=%7be46c3c48-e880-4b98-87d2-8fbdace4873d%7d
Toxocara spp.	74 www.dpd.cdc.gov/dpdx/HTML/Toxocariasis.htm gsbs.utmb.edu/microbook/ch091.htm
Baylisascaris spp.	108 www.dpd.cdc.gov/dpdx/HTML/Baylisascariasis.htm picasaweb.google.com/idintl/ParasitologyVolume2ForWeb#5195057361849894386
Paragonimus spp.	129 www.dpd.cdc.gov/dpdx/HTML/Paragonimiasis.htm http://picasaweb.google.com/idintl/ParasitologyVolume1ForWeb#5177598086916071954
Trichinella spp.	191 www.dpd.cdc.gov/dpdx/HTML/Trichinellosis.htm gsbs.utmb.edu/microbook/ch091.htm
Hydatidosis	www.dpd.cdc.gov/dpdx/HTML/Echinococcosis.htm www.pucrs.br/fabio/atlas/parasitologia
Coenurosis	130 www.scielo.br/scielo.php?script=sci_arttext&pid=S0103–84782008000400021&lng=e&nrm=iso&tlng=e
Strongyloides spp.	www.dpd.cdc.gov/dpdx/HTML/Strongyloidiasis.htm
Filariasis	www.dpd.cdc.gov/DPDX/HTML/ImageLibrary/Filariasis_il.htm www.eyepathologist.com/disease.asp?IDNUM=345150
Myiasis	www.dpd.cdc.gov/DPDx/html/ImageLibrary/M-R/Myiasis/body_Myiasis_il5.htm

since most of the data come from uncontrolled studies or clinical reports of a few patients (51, 127, 230, 281, 293).

Combinations of anthelmintics with anti-inflammatory agents have been investigated in animal models with positive results. The following combinations have been implemented: albendazole and thalidomide (42), mebendazole and interleukin 12 (85), and albendazole with extract from the Chinese medicinal herb *Artemisia capillaris* (157). Evidently, the key issue in treat-

TABLE 3. Immunological methods for diagnosis of cerebral angiostrongyliasis

Targets	Method	Sensitivity (%)	Specificity (%)	Reference(s)
91-kDa antigen	Antigen detection, ELFA[a]	88 (serum) 100 (CSF)	NR[b] NR	257
29- and 31-kDa antigens	ELISA, crude female antigen	100	67	208
	WB, 31-kDa protein	69	83	
	WB, 29-kDa protein	NR	"Low"	
204-kDa antigen	ELISA, antigen detection	NR	"High"	57, 58
	ELISA-PCR, antigen detection	98	100	
29-kDa antigen	WB	56 (serum + CSF)	99 (serum + CSF)	131, 145, 179
	WB, IgG4	75 (serum)	95 (serum)	
	WB (serum) and ELISA (CSF)	80 (serum + CSF?)	NR	
31-kDa antigen	Dot blot	100	100	87
32-kDa antigen	ELISA	"High"	100	165
15-kDa antigen	ELISA, antigen detection	87	100	167
100- to 3-kDa antigen	Dot blot	100	86	89

[a] ELFA, enzyme-linked fluorescent assay.
[b] NR, not reported.

ment of angiostrongyliasis is the control of inflammation. There is an urgent need for extensive studies of new approaches to chemotherapy and evaluation of neurological relapses (187, 249).

GNATHOSTOMIASIS

The Parasite

Gnathostoma is another nematode capable of causing eosinophilic meningoencephalitis, known as gnathostomiasis. This worm has a cephalic bulb covered with transverse rows of recurved hooks that are larger and more flattened than those on the body, and its entire body surface is covered by regular rows of spines. The male's tail lacks a caudal bursa. Transmission to humans occurs indirectly through copepods and vertebrates, which act as intermediate hosts. Adults live in the stomachs of carnivorous mammals, such as pigs. Humans are accidental hosts for larvae.

History

The genus *Gnathostoma* was first described by Owen in 1836 as cylindrical, 3-cm-long worms with bodies covered by regular rows of spines, living in the gut of vertebrates. *Gnathostoma spinigerum* was found in specimens from the stomach wall of a tiger in a London zoo. This worm was also identified as a cause of CNS infection in humans in several reports from several east Asian countries, including Japan and China. Other *Gnathostoma* species have been reported in Japan (*G. doloresi*, *G. nipponicum*, and *G. hispidum*) and Mexico (*G. doloresi*). *Gnathostoma* causes cutaneous larva migrans syndrome (CLM) and typically does not frequently affect tissues other than the skin (78, 202). The description of retrieval of this parasite from a patient with fatal encephalomyelitis in 1967 was the first report of *Gnathostoma* as a cause of human CNS infection (24, 47).

Life Cycle and the CNS

Initially, *Gnathostoma* eggs are released into the water from the feces of natural hosts. After molting once inside the egg, the larvae hatch at second stage. Then, larvae are ingested by the first intermediate host (*Cyclops*), a crustacean copepod, where they molt into L3 larvae. Later, in a second intermediate host, such as a freshwater fish or frog, the larvae develop to the advanced infectious L3 stage. Birds, reptiles, and mammals may act as paratenic hosts and become infected without further development of the larvae. The definitive host becomes infected by feeding upon any of the intermediate hosts or paratenic hosts. Humans may become infected by ingestion of contaminated flesh of the second intermediate host or paratenic hosts or through contaminated water. The larvae penetrate the human gut wall and migrate through the peritoneal cavity to the liver. From there, they continue to multiple tissues or entire organs, such as the CNS, the eye, and subcutaneous tissues, without fully developing to adult worms (13, 120).

Epidemiology

Gnathostomiasis mainly affects young male adults in the third and fourth decades of life and is known to have a seasonal occurrence corresponding to the rainy season in Thailand (231). Although the occurrence of human gnathostomiasis is well known in Asian countries, especially Thailand, Korea, and Japan, the CLM caused by *Gnathostoma* species (possibly *G. binucleatum*) has been detected mainly in Mexico and other Latin American countries, such as Ecuador and Peru (40, 79).

Humans become infected with *Gnathostoma* species by eating raw fish, snails, shrimp, vegetables, poultry, pigs, snakes, and frogs. Less common modes of infection are ingestion of water containing infected copepods and penetration of advanced L3 larvae through the skin of food handlers. Feeding habits should be carefully investigated, since larvae can remain in the tissues for a long time prior to migration to the CNS, resulting in long incubation periods (193, 237).

Gnathostomiasis has become an important concern in travel medicine, since several reports of both cutaneous and CNS diseases in patients coming from classical areas of endemicity have been published (193, 237, 261). Presumptively "exotic" food can now be found in restaurants and specialized markets all around the world (38). Proper food handling minimizes infection, as larvae can be killed by boiling for 5 min or freezing at −20°C for at least 3 days (252).

Disease

Initial symptoms caused by penetration of advanced L3 larvae through the gut wall can include abdominal or epigastric pain, anorexia, malaise, vomiting, diarrhea, urticaria, and fever (231). These prodromes usually do not last more than 5 days. Concomitant with localization of larvae in the liver, abdominal pain may localize in the right upper abdominal quadrant. Migration in subcutaneous tissues induces a linear dermatitis with light to moderate pruritus, usually localized to the abdomen and later in multiple skin areas, known as creeping eruption or CLM. In addition to linear dermatitis, when *Gnathostoma* larvae reach the subcutaneous fat in humans, a classical presentation is a migratory panniculitis consisting of an erythematous, deeply seated, ill-defined nodule or plaque, accompanied by itching and occasional pain, located on the trunk or periphery of the body. Similar lesions will recur a few centimeters beyond the original location. The erratic migration of L3 larvae may result in CNS or eye infection. The incubation period is approximately 4 weeks, but there are some indications that it may last 3 or more months (231, 174). Dormant larvae are known to persist for many years, leading to very long incubation periods or recurrence (237).

A common CNS impact of gnathostomiasis is radiculomyelitis, which is characterized by sharp sudden nerve root pain emanating from the spine to the trunk, limbs or perineum. This pain is often followed by paresis and paralysis of extremities, and sometimes urinary incontinence. A second important CNS impact is specific to the encephalus and involves severe headache, impairment of sensorium, neck stiffness, convulsions, and vomiting. Some patients have these encephalitic manifestations together with hemiparesis and hemiplegia of one or both limbs (24, 231). Although

TABLE 4. Immunological methods for diagnosis of gnathostomiasis[a]

Target	Method(s)	Sampe material (type)[b]	Sensitivity (%)	Specificity (%)	Reference
Crude L3 antigen	ELISA (IgG)	Serum (4 cutaneous + 10 CNS)	Overall, 59; CNS, 100	Overall, 84; CNS, NR	273
Crude L3 antigen	ELISA (IgG)	Serum (46 cutaneous)	100	NR	77
Crude antigen	Somatic antigen ELISA	Serum	87	96	178
	ES antigen ELISA		87	97	
Crude antigen	*G. doloresi* ELISA (IgG)	Serum (299 cutaneous + 1 ocular)	93	98	79
24-kDa antigen (pI 8.5)	WB	Serum	100	100	206
23- to 25-kDa antigen (pI 8.3–8.5)	Two-dimensional PAGE and WB	Serum	83	100	301
Crude L3 antigen	ELISA (IgG and isotypes)	Serum (cutaneous)	IgG1: 98	IgG2: 88	209
21-kDa antigen	ELISA (IgG4)	Serum (11 cutaneous; 2 ocular; 1 peritoneal)	100	100	6
24-kDa antigen	ELISA (IgG4)	Serum (11 cutaneous; 2 ocular; 1 peritoneal)	93	93	6
100- to 3-kDa antigen	Dot blot	Serum (10 cutaneous)	100	100	89
24-kDa antigen	WB, isotypes	Serum	IgG, 91; IgG1, 66; IgG4, 75	IgG, 97; IgG1, 98; IgG4, 94	161

[a] PAGE, polyacrylamide gel electrophoresis; NR, not reported.
[b] In cases where the information was available, data in parentheses include number of patients and type of infection with *Gnathostoma* species: cutaneous, ocular, CNS, or peritoneal.

isolated subarachnoid hemorrhage is not the usual presentation of gnathostomiasis, hemorrhagic lesions are common and are a main factor in mortality.

Diagnosis

A bloody and xanthochromic CSF is highly suggestive of gnathostomiasis and is a particularly helpful criterion for differentiating from meningitis caused by *A. cantonensis* (see above). Eosinophilia is not always present in peripheral blood but is very common in the CSF. In two studies from Thailand with large numbers (24 and 162) of patients (24, 231), CSF eosinophilia (>10%) was detected in 74% and 100% of patients, respectively. In the same studies, CSF eosinophilia >30% was detected in 64% and 65% of patients. Protein levels were elevated in two-thirds of patients, and glucose levels were unchanged or only slightly reduced (24, 231).

Upon MRI examination of the spine, lesions may appear as diffuse or segmental enlargement, with or without postgadolinium linear enhancement. Hyperintense micronodular or fuzzy lesions on T2-weighted brain images, with or without enhancement, can suggest intraparenchymatous or intraventricular hemorrhage (38, 237, 250, 251). Although only a small number of reports with MRI examination are currently available, the description of focal brain lesions or segmental or nodular enlargements in the spine should be considered an important aspect for differentiation from angiostrongyliasis.

It is unusual to detect L3 larvae in the CSF. These larvae are 2.8 to 5.2 mm long and 0.3 to 0.8 mm wide, and, like adult worms, their body surface is covered by spines. When biopsy or necropsy specimens are examined, the presence of spines or hooks in regular rows, as well as the identification of the cephalic bulb, allows the definitive diagnosis of gnathostomiasis (Table 2).

Serological techniques have evolved from the use of crude antigenic preparations to that of partially purified or single antigenic components (Table 4). Historically, most methods were evaluated for detection of antibodies in serum of patients with cutaneous disease. Detection of antibodies in CSF was evaluated in only a very small number of patients with apparent high sensitivity (273, 284). As the detection of antigen or immune complexes is considered less reliable, the detection of antibodies at the class or isotype level is a promising approach (6, 195, 284). However, significant cross-reactivity has been demonstrated in several antibody detection systems testing serum samples from patients infected with *A. cantonensis*, hookworms, *Strongyloides stercoralis*, *Trichuris trichiura*, *Capillaria philippinensis*, *Wuchereria bancrofti*, and *Opisthorchis viverrini* (89, 209).

Antigen detection methods have been used for L3 larva confirmation. A 24-kDa glycoprotein specific to L3 is a promising antigen for diagnosis, with sensitivities ranging from 100% in ELISA to 75% for immunoglobulin G4 (IgG4) in WB. The specificity of this method ranges from 100% in ELISA to 93 to 94% for IgG4 in ELISA or immunoblotting (6, 161, 206). There is also a 21-kDa antigen with 100% sensitivity and specificity in an IgG4 ELISA that deserves more extensive evaluation (6).

Treatment

For the treatment of cutaneous gnathostomiasis, both albendazole and ivermectin are reported as effective therapies, but no anthelmintic agent or corticosteroids have been formally evaluated for the treatment of CNS disease (150, 151, 204). Alongside these curative therapies, radicular pain and headache require supplemental symptomatic and supportive treatment. Though full recovery can be expected in most instances, the prognosis for neurological disease caused by *G. spinigerum* is poor. Mortality with this infection is in the range of 12 to 15%, and permanent sequelae, such as paraplegia, radicular lesions, cranial nerve lesions, and hemiparesis, remain in 23 to 46% of patients (231, 253).

SCHISTOSOMIASIS

The Parasite

Among the trematodes, the superfamily Schistosomatoidea includes flatworms that parasitize the blood vessels of vertebrates and develop larval stages in mollusks. Other distinctive features of the Schistosomatoidea are sexual dimorphism, lack of a muscular pharynx, and production of nonoperculated eggs. Within the genus *Schistosoma*, five species are known human parasites: *S. mansoni*, *S. haematobium*, *S. japonicum*, *S. mekongi*, and *S. malayensis.* The CNS is an ectopic location for eggs of *Schistosoma* species, and although the condition has been fully characterized only for *S. mansoni*, other species may also involve the CNS. While *S. mansoni* is a focus in this review, its pathogenesis and clinical features are usually similar to those of *S. haematobium* or other species (160).

History

In 1851, Theodor Bilharz found a trematode inside the mesenteric veins of a young Egyptian and incorrectly considered the eggs with lateral and terminal spines an intraspecific variation. Sambon proposed the new species as *Schistosoma mansoni* in 1907, and it was fully described by Pirajá-da-Silva a year later, in Salvador, Brazil. Interestingly, in 1910, Rufer found calcified eggs in the kidneys of Egyptian mummies of the 20th Dynasty (1250 to 1000 BCE), but there are even more ancient (3000 BCE) molecular indications of human infection (188).

Life Cycle and the CNS

The female worms migrate to distal mesenteric veins to lay eggs, which cross the intestinal wall and eventually reach the feces. An egg must be in water to hatch and release the miracidium, which is a ciliated larva that actively swims and penetrates into the tegument of snail intermediate hosts. Thousands of cercariae with bifurcated tails are generated after asexual reproduction of the parasite in the mollusk. The infective cercariae are released into water after stimulation by light and penetrate into the skin of vertebrate hosts, including humans. The cercaria transforms into a schistosomulum immediately after skin penetration and migrates to the lungs via the venous circulation. The schistosomulae break out from the lungs and are finally carried to the portal system through the left side of the heart (147). Given this progressive cycle, the presence of eggs in the CNS is unexpected. There are two possible explanations for the presence of eggs in CNS: (i) the anomalous migration of the worms laying eggs next to the CNS and (ii) embolization of the eggs (223, 225, 255).

Epidemiology

Schistosomiasis affects 200 million people, and 600 million are at risk of infection. Areas of endemicity where people are at risk include 74 countries, mainly in sub-Saharan Africa and Latin America and also Egypt and China (48). Although morbidity has been reduced in many countries, the infections are geographically spreading to new foci, which makes this an important problem in travel medicine (156, 201). Neuroschistosomiasis (NSM) is apparently associated with light infections and is primarily associated with people from areas where the parasite is not endemic traveling in and out of areas of endemicity (94). But it may also be the case that NSM has been underdiagnosed in countries of endemicity where medical attention has been focused on the large numbers of patients with more severe cases of intestinal and hepatic lesions (160, 201). NSM is most common in young male adults.

Disease

The initial phase of schistosomiasis infection is generally asymptomatic. However, an important form of dermatitis can be used for differential diagnosis. It is known as "swimmer's itch," a punctiform pruriginous dermatitis caused by penetration of cercariae. The name is derived from the particular distribution in areas of skin that has been submerged in contaminated water.

In NSM, spinal lesions predominate (203). The valveless epidural Batson's vertebral venous plexus connects the portal venous system and inferior vena cava to the spinal cord and cerebral veins. Portal hypertension may open up more channels for egg embolization. This anatomic consideration is relevant to explain the characteristic involvement of the medulla below T5, particularly at T11 to L1 (94). NSM can ensue in the initial phase of the infection or at any phase, but with a low parasitic burden. For example, in a study of 63 patients, 72% had fewer than 1,000 eggs/g of tissue in rectal biopsy fragments (93). A very active and modulated granulomatous reaction involves the egg and may produce inflammatory tumors with secondary meningeal involvement. Besides the pivotal role of the egg in pathogenesis, the reactivity of the host is also fundamental to explain the spectrum of clinical severity.

For the spectrum of clinical manifestations of NSM, Ferrari and colleagues (93) have proposed the following classification: (i) medullar, when the involvement of the spinal cord predominates; (ii) myeloradicular, when spinal cord and nerve root lesions occur; and (iii) conus-cauda equina syndrome, when there is a predominant involvement of the terminal spinal cord and cauda equina. Symptoms and signs show acute or subacute progression. Back pain is the most common initial symptom, but it can persist as undiagnosed NSM because of its wider prevalence caused by chronic fibromyalgia and stress. Other symptoms include lower limb weakness, bladder dysfunction, paresthesias, sensory disturbances, deep tendon abnormal reflexes, constipation, and sexual impotence. Involvement of nerve roots, particularly the cauda equina, is quite common in NSM (94). It is noteworthy that patients usually do not carry lesions in more commonly affected organs, such as liver, intestines, and lungs. Encephalomyelitis as part of a systemic hypersensitivity reaction during the initial phase of the infection and granulomatous brain masses with the presence of eggs are very rare and are not associated with eosinophilic CSF pleocytosis (255). Thus, NSM should be suspected with evidence of low thoracic, lumbar, or sacral spinal lesions and the presence of eggs in other tissues or feces, alongside the exclusion of other causes of myeloradicular damage.

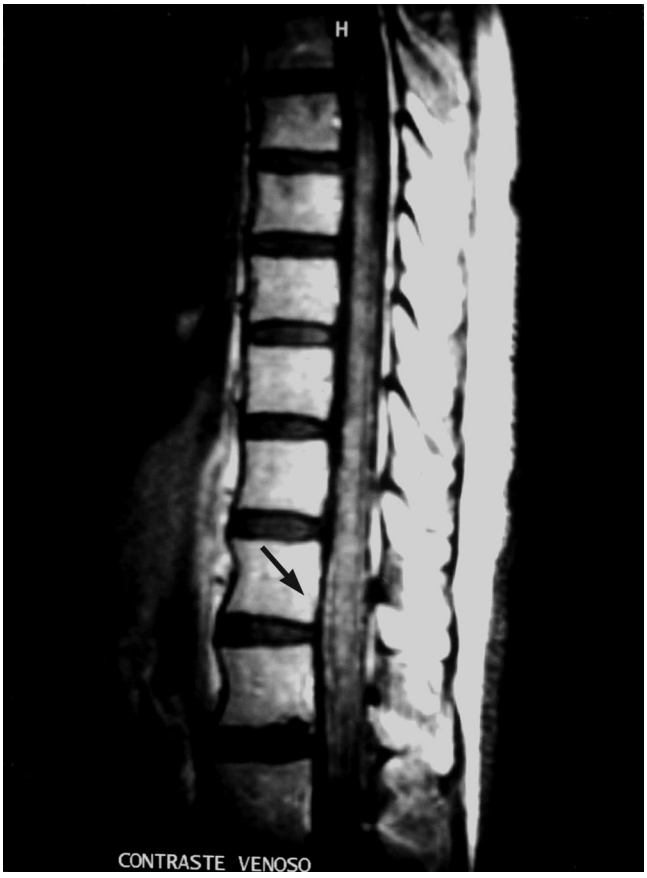

FIG. 3. Enlargement (arrow) of the conus medularis with micronodulations in spinal cord schistosomiasis. (Reproduced from reference 260 with permission of the publisher.)

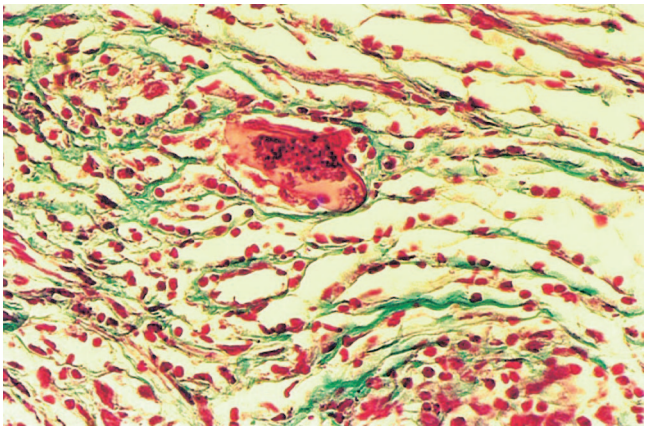

FIG. 4. *S. mansoni* egg in the spinal cord of a patient with myeloradiculopathy. The eggs have a lateral spine and are large structures (114 to 180 μm long by 45 to 70 μm wide). (Reprinted from reference 260a with permission of the publisher.)

Diagnosis

MRI of schistosomiasis patients shows enlargement of the spinal cord and thickening of the spinal roots, including the cauda equina on T1-weighted images. In general, signal hyperintensity on T2-weighted images and a heterogeneous pattern of enhancement with contrast material are the most prominent features in MRI. Conventional myelography and computer-assisted myelography are less sensitive than MRI but may also show the enlargement of the spinal cord or nerve roots (Fig. 3) (160).

CSF samples from schistosomiasis patients show a mild to moderate increase in cells and protein content. Glucose levels are slightly low or normal, and eosinophilia is evident in 50% of the patients (93, 197). Failure to detect CSF eosinophilia has been attributed to lack of identification of eosinophils when a stained preparation of the sediment is not examined (222).

ELISA performed with soluble egg antigen (SEA) is the more reliable immunological method for diagnosis of NSM, with 56% sensitivity and 95% specificity (95). Although more purified preparations and defined antigens have been reported, they have not been extensively tested for diagnosis of NSM (81, 234). Ferrari and colleagues (95) have proposed CSF diagnostic criteria based on the concentration of IgG anti-SEA in CSF. Specifically, a value of 0.1 μg/ml IgG anti-SEA excludes the possibility, and 1.4 μg/ml of IgG anti-SEA supports the possibility of schistosomiasis.

Antibody detection methods are not considered useful in areas of endemicity, because these areas contain a large number of serologically positive but not diseased individuals (36). However, for the diagnosis of NSM, immunological methods are relevant because this disease is characterized by antibody production localized to the CSF. Seroconversion is likely valuable for the diagnostic workup (247).

The use of purified antigens, the study of class or isotype response, and extensive standardization studies are necessary to improve molecular diagnosis in NSM. Typically, confirmed diagnosis is made by demonstration of typical large *Schistosoma* sp. eggs on histological sections of the granulomatous lesions as well as in stool or urine samples (Fig. 4 and Table 2). However, biopsy or surgical resection is not recommended because of the risk of adding damage to neural tissues.

Treatment

Praziquantel (PZQ) and corticoids are the drugs of choice for neuroschistosomiasis treatment, although there is no consensus regarding total doses or duration of the treatment (68, 160, 259). PZQ should be administered at 50 to 60 mg/kg either as a single dose (260) or as a daily dose for 5 days (94). Corticoids should be maintained for long periods, such as 3 to 6 months. Clinical improvement should begin 24 to 48 h after initiation of corticoid treatment, and these drugs should be initiated as soon as NSM is suspected. PZQ may be initiated some time later, but an anthelmintic drug should always be used, to avoid clinical relapses (41). The prognosis is good: 70% of the patients recover completely (94). MRI is a good method for evaluation of response to treatment (259).

CYSTICERCOSIS

The Parasite

Cysticercosis is the infection with the larval stage of *Taenia solium*, and neurocysticercosis (NCC) occurs when these cysts are located in nervous tissues. *T. solium* is a flat metazoan organism belonging to the phylum Platyhelminthes, the class Cestoidea, and the order Cyclophyllidea. Humans are the definitive host, and herbivorous animals act as intermediate hosts to this worm, commonly known as tapeworm.

History

Historical references to what is known today as cysticercosis date back to antiquity. Aristotle described the characteristics of the infection. In 1697, Malpighi described cysticerci as segments of a worm. The genus *Cysticercus* was proposed in 1800 by Zeder, and by 1885, Kuchenmeister had experimentally demonstrated that ingestion of cysticerci gives rise to the tapeworm, *T. solium*. As a point of reference, the taxon *Cysticercus cellulosae* is invalid under the current rules of zoological nomenclature.

Life Cycle and the CNS

Tapeworms fixate their scolex at the mucosa of the human small intestine and produce proglottids packed with eggs that are released with feces. Pigs are the intermediate hosts of *T. solium*, and they become infected by ingestion of the eggs. Inside the pig, the embryo (onchosphere) is released from the egg and penetrates the intestinal wall, where it migrates through blood vessels to other body tissues. At the destination tissue, a cystic larval stage (the cysticercus) develops with a single protoscolex. Cysticerci are found mainly in striated muscles, subcutaneous tissue, the eye, and the CNS. Ingestion of undercooked pork containing these cysticerci allows the tapeworm to complete the cycle. After ingestion of tissue containing cysticerci, protoscolices evaginate from the cysticerci and fixate themselves on the human intestinal mucosa. Humans are an exclusive definitive host for *T. solium* but are actually an accidental intermediate host for the larval stages of the parasite.

Epidemiology

Although no gender preference has been suggested, the disease appears to be more severe in women. There is a hypothesis that female hormones exacerbate the outcome (101). Peak age incidence is found in middle-aged adults (267).

Infection with *T. solium* and cysticercosis are probably more widespread than what is known from reports in the literature. The countries with the largest prevalence of NCC are Mexico and India. Infections are also prevalent in other countries of Latin America, Africa, and Asia.

Cysticercosis is acquired by ingestion of eggs released with feces, not by ingestion of undercooked pork. A frequent mistake in reports of clinical cases is to exclude the possibility of NCC, due to underreporting of eating raw pork. Good sanitation and health education are key measures to ensure elimination of this disease. With humans as the source of infection, patterns of transmission may arise within social clusters.

Disease

NCC is neither a febrile disease nor a typical meningitis syndrome (267). Progression of clinical manifestations is slow and confusing. Symptoms and signs depend on localization, number, size, developmental stage, and type of the cysticerci. Host reaction to the presence of the parasite is also a key determinant in pathogenesis. Between 70 and 90% of patients present with seizures, and this parasitic infection is considered the most important cause of late-onset epilepsy in areas of endemicity (107, 216). Contrary to seizures derived from other etiologies of acquired epilepsy, NCC seizures are usually not simultaneous with focal neurological signs (267). Intellectual impairment and behavior disorders may also be manifestations of NCC (184, 213). Meningeal irritation depends on cysts located next to or within the subarachnoid space.

Cysts in the subarachnoid space or within the ventricular system may lead to the obstruction of CSF flow and to acute intracranial hypertension, with focal neurological signs. Intraventricular cysts occur in 20% of patients, and the fourth ventricle is the most commonly affected. With fourth-ventricle blockage, there are often signs of brainstem dysfunction due to the compression of the ventricular floor. Mobile intraventricular cysts may result in sudden death or acute intermittent hydrocephalus and hypertension, with bursts of headache, positional vertigo, and loss of consciousness related to abrupt movements of the head. Giant cysts, bunches of growing cystic membranes, and "racemose" cysticerci are considered malignant forms of NCC that result in high lethality and that usually involve invasion of the basal cisterns (224).

The spinal cord is involved in less than 5% of NCC cases, and this involvement leads to compression syndromes or meningomyelitis, manifested by sphincter disturbances and progressive weakness of the extremities. In cases with spinal involvement, 30% of patients have concomitant brain cysts (256).

Small numbers of intraparenchymal cysts are usually asymptomatic, and their presence carries a good prognosis. The true frequency of patients with this form of the disease in the general population is unknown. Occasional findings in autopsy studies range widely, from 43 to 91% (46, 297).

Diagnosis

Live and uncomplicated cysts are spherical lesions measuring approximately 1 cm. By computerized tomography (CT) or MRI, it is possible to identify the presence of a small dot inside the cyst that corresponds to the invaginated scolex, or protoscolex. When cysts degenerate, they are surrounded by edema and a ring enhancement. Calcification may ensue both around and within the lesion at a final stage. Due to isodensity, intraventricular cysts are seen only by MRI scans. CT is still the first line of image examination, since it reveals the cysts and calcifications, a feature not well demonstrated by MRI. This makes CT a crucial diagnostic tool for NCC.

The CSF of NCC patients shows mononuclear pleocytosis and eosinophilia. Cell counts rarely exceed 300 per mm^3. Pro-

TABLE 5. Immunological methods for the diagnosis of cysticercosis in CSF samples[a]

Target	Method	Material	Sensitivity (%)	Specificity (%)	Reference
Fractions, saline/SDS	ELISA	CSF	Tso-NaCl: 100 Tcra-NaCl: 85 Tso-SDS: 95 Tcra-SDS: 87	Tso-NaCl: 100 Tcra-NaCl: 100 Tso-SDS: 100 Tcra-SDS: 97	12
Antigen	ELISA	CSF			218
	Anti-Tso		81	82	
	Anti-Cra		90	98	
	Anti-Cra, <30 kDa		95	100	
ES antigens	ELISA	CSF	92	97	192
14- and 18-kDa antigens	ELISA	CSF	100	100	217
14-kDa antigen	ELISA	CSF	95	100	221
Peptides HP6-2 and Ts45W-1	ELISA	CSF	93	85	100
14 and 18-kDa antigen	ELISA	CSF and serum	100	100	91
10-kDa antigen, recombinant	ELISA	CSF	91	NR	162
		Serum	97	96	
14-kDa antigen, recombinant	ELISA	CSF	100	100	69
		Serum	97	100	
Fractions: 47–52, 64–68 and 70 kDa	WB	CSF	100	NR	11
		Serum	80	NR	
Crude antigen (W) and VF, Tso and Tcra	ELISA	CSF	TsoW, 91; TcraW, 87; TsoVF, 91; TcraVF, 91	TsoW, 94; TcraW, 94; TsoVF, 97; TcraVF, 97	274

[a] Tso, *Taenia solium*; Tcra, *Taenia crassiceps*; NaCl, saline extract; SDS, sodium dodecyl sulfate extract; W, worm; VF, vesicular fluid; NR, not reported.

teins in CSF are elevated within the range of 50 to 300 mg/dl, and glucose levels are usually normal (267).

Immunological diagnosis of cysticercosis has mainly been made with antibody detection by ELISA and WB. There is a long list of antigens that have been evaluated, in both crude and purified forms (Tables 5 and 6). WB with purified cysticercus glycoprotein antigens is the current "gold standard" antibody detection assay, and three to five main components have been evaluated as synthetic or recombinant peptides, with exceptional performance in serology (134, 248, 282) (Tables 5 and 6). The use of these peptides to detect antibodies in the CSF is expected to reproduce what has been well demonstrated in serum. Immunological tests are more successful with CSF samples, but results are dependent upon the activity of the infection. Inactive cysticerci are usually associated with very low reactivity (162, 192). Immunofluorescence and complement fixation (CFA) tests are much less sensitive and specific than ELISA and WB, especially with use of purified antigens (30).

The use of other recombinant antigens (54, 96) or synthetic peptides (100), examination of isotypes such as IgG4 (55), the use of tertiary conformational alterations (227) or multiepitope chimeric proteins (245) and other novel strategies may further improve immunological detection methods.

Nucleic acid detection by PCR was positive in the CSF of 29 out of 30 patients with NCC (5). Identification of *Taenia* species is possible in feces and in tissues by restriction fragment length polymorphism analysis, base excision sequence scanning, thymine-based analysis, and multiplex PCR (305).

In 2000, a panel of experts convened in Peru and proposed diagnostic criteria for NCC. The following criteria are now considered absolute: histological demonstration of the parasite from biopsy of a brain or spinal cord lesion (Table 2), cystic lesions showing the scolex on CT or MRI, and direct visualization of subretinal parasites by funduscopic examination. The isolated presence of one absolute criterion or different combinations of major, minor, and epidemiologic criteria supports two degrees of diagnostic certainty: definitive or probable di-

TABLE 6. Antibody detection immunoassays for the diagnosis of cysticercosis in serum samples[a]

Target	Method	Sensitivity (%)	Specificity (%)	Reference(s)
10- to 24-kDa glycoproteins	ELISA and WB	100	NR	134
10-kDa protein, recombinant	ELISA	97	98	54
Chimeric antigen (Ag1V1/Ag2), recombinant	ELISA	90	NR	244, 245, 246
Crude antigen, fraction VF	ELISA	Tso-VF, 100; Tcra-VF, 100	Tso-VF, 90; Tcra-VF, 96	30
8-kDa protein (TsRS1)	WB	100	100	117
GP50, recombinant	WB	100	100	119
Crude andtigen, fraction VF	ELISA	Tso-VF, 91; Tcra-VF, 91	Tso-VF, 96; Tcra-FV, 95	9
T24, recombinant	WB	94	98	118
Ts8B1-3, Ts8B2, recombinant	ELISA	96	93	96
20- to 24-kDa protein	ELISA	86	100	180
	Dot blot	86	98	

[a] NR, not reported; Tso, *Taenia solium;* Tcra, *Taenia crassiceps*; VF, vesicular fluid.

agnosis. For details, see the report of the consensus meeting (73).

Treatment

The therapeutics of NCC varies according to the clinical situation. Corticoids may be necessary with the inflammatory clinical forms, such as meningitis and co-occurrence of NCC with vasculitis. Corticoids are mandatory treatment for large intraventricular cysts and encephalitis (236); the recommendation is dexamethasone, 4 to 30 mg/day, or prednisolone, 1 mg/kg/day, as long as necessary. Adequate seizure control may require antiepileptic drugs. Ventricular shunting is required for persistent hydrocephalus. Surgical removal is necessary to relieve life-threatening giant and/or racemose cysts, or cysts producing significant compression syndromes. Advances in diagnostic tools, such as imaging methods and immunological detection, have improved surgical treatment approaches (61).

Albendazole (15 mg/kg/b.i.d. for 8 days) is the drug of choice for the treatment of NCC in symptomatic patients with multiple live brain parenchymal cysticerci. PZQ is an apparently less effective alternative (275). In cases of inflamed and degenerated or calcified cysts, albendazole is not indicated for treatment. As in other CNS parasitic infections, there are concerns about sudden degradation of the cysts, which may exacerbate inflammatory lesions (35, 72).

Hydrocephalus and intracranial hypertension occur in 60% of patients, and these are the main indicators of poor prognosis. Mortality is 50%, and most patients die within 2 years after a shunt is implanted (276). Intraventricular cysts are prone to cause further complications and high mortality (66). Recurrence of seizures is common and does not necessarily represent failure of anthelmintics, since usually only calcified nodules are detected (267).

TOXOCARIASIS

The Parasite

The superfamily Ascaridoidea includes cylindrical worm parasites of vertebrates, whose larvae migrate in host tissues on their way to becoming adults inside the gut lumen. *Ascaris lumbricoides* is a well-known enteroparasite of humans. *Ascaris* and *Toxocara* species have very similar morphologies, habitats, and life cycles. In the genus *Toxocara*, there are the ascarids of dogs (*T. canis*) and cats (*T. cati*), which measure between 7.5 and 12.5 cm and exhibit characteristic cervical alae. Among felids, parasitic larvae of *T. cati* and *Toxascaris leonina* do not have the same migration behavior and preference for nervous tissue shown by *T. canis*, which may explain the prominence of *T. canis* as a cause of CNS infections.

History

Toxocara specimens were initially described by Werner in 1782, but the genus was not established until 1905 by Stiles (302). Human infection was first documented in the 1950s, when Wilder discovered a larval nematode within a retinal granuloma of a child (298). Around the same time, Beaver and colleagues described what today is called "visceral larva migrans" (VLM), a severe multisystem disease with eosinophilia caused by migrating larvae of the *Toxocara* species (15). In 1951, a larva was found for the first time in the brain of a patient, and it was subsequently proven to be *T. canis* (14). In 1958, Sprent gave the first detailed description of the life cycle of *T. canis* (268).

Life Cycle and the CNS

Adult *T. canis* lives in the lumen of dog intestine and produces eggs, which are eliminated in feces. Eggs are thick-walled and can remain in the environment for a long period of time before they embryonate and become infective. When the eggs are ingested by dogs, L2 larvae are liberated and penetrate the intestinal wall. Larvae travel through the circulatory system to the liver and lungs. From the lungs, they crawl up the bronchial tree and re-enter the digestive system, where they develop into adults. Persistence of larvae in the tissues leads to the most common mode of infection in dogs: vertical transmission through the transplacental route. The persistence of larvae in nonusual paratenic hosts, such as mice, rats, and monkeys, is another source of infection, because the larvae are ingested by wild canids and felids with their prey (268). In cats, no transplacental infection occurs with *T. cati*, but transmission to offspring does occur via milk. Infection through the ingestion of paratenic hosts is also common in cats (75).

In accidental hosts such as humans, as larvae persist in the tissue and wander outside their usual route, they may eventually reach multiple organs, like the eyes and the CNS. Although CNS infection in humans is rare, *T. canis* larvae are neurotropic in experimental infections of primates (111). Experimental infections of mice with *T. canis* indicate that it accumulates in both body muscle and brain tissues after 1 week postinfection, but experiments with *T. cati* show that accumulation is restricted to muscle.

Epidemiology

Toxocariasis is a cosmopolitan parasitic infection. Seroprevalence is highly variable, but children are considered the most likely exposed population, due to outdoor activities and frequent contact with dogs and cats (75, 97). Interestingly, there is not a clear association of human toxocariasis with the presence of pets in the house, probably because contaminated outdoor areas are the main source of infection (45). Infective *Toxocara* eggs can remain viable for months or years in the environment, which increases the chance for their dissemination by paratenic hosts or by rain and wind (75). The contamination of drinking water supplies can lead to waterborne outbreaks (16).

Disease

Human toxocariasis manifests as either VLM or ocular larva migrans syndrome. Ocular infection is considered a compartmentalized infection, and patients may present isolated ocular larva migrans syndrome.

CNS infection is rare, and pure meningitis is also rare. Reports of not more than 50 patients with neurotoxocariasis can be found in the literature, and in many reports the diagnosis was only presumptive. For example, diagnoses have been made

TABLE 7. Immunological methods for diagnosis of toxocariasis in serum

Target	Method	Sensitivity (%)	Specificity (%)	Reference
TES	Dot blot	95	97	32
	ELISA	95	90	
30-kDa protein, recombinant	ELISA, TES	TES: 100	TES: 57	304
	ELISA, 30-kDa antigen	30-kDa protein: 100	30-kDa protein: 97	
120-kDa protein, recombinant	WB	100	100	102
TES	ELISA (IgG)	IgG: 97	IgG: 45	205
	ELISA (IgG4)	IgG4: 36	IgG4: 78	
TES	Dot blot	100	85	240
	ELISA	100	70	
57-kDa protein	Sandwich ELISA	90	100	128
30-kDa protein, recombinant	ELISA (IgG4)	92	89	207

based on the presence of neurological dysfunctions and eosinophilia and negative serology for other parasitic causes, such as angiostrongyliasis, combined with a pattern of close contact with dogs. Some authors give too much value to positive responses to anthelmintic treatment and consider it supportive of a presumptive diagnosis. With so little rigorous data from drug trial treatment of CNS toxocariasis and several cases of spontaneous remission, only tentative conclusions can be drawn from the reported outcomes.

The CNS impact of toxocariasis is manifested as meningitis (36%), myelitis (28%), encephalitis (62%), or some combination (90). Other rarer clinical presentations of CNS impact are extramedullary tumor, brain vasculitis, seizure, and isolated behavior disorder (289).

In Sprent's early descriptions of the parasite impact on human disease in 1958, he suggested that toxocariasis facilitates viral or bacterial infection, similar to infections with *S. mansoni* and *S. stercoralis* (159). Data from a recent case-control study have not supported this association with toxocariasis (199).

Diagnosis

MRI images of toxocariasis patients may show multiple or solitary subcortical, cortical, or white matter lesions, which are T2-weighted hyperintense and homogeneously enhanced after contrast administration. Spinal cord involvement with tumoral lesions is also usually hyperintense at T2 upon MRI and shows strong enhancement (303).

It is rare to find larvae in the CSF (289, 290) or tissue, as illustrated by a report of one single larva within 100 sections from a biopsy fragment (302). L2 larvae are 290 to 300 by 18 to 21 μm. Due to their small dimensions, these larvae are especially difficult to detect in transverse biopsy sections (Table 2). The general characteristics of a nematode larva in histological sections include a chitinous envelope and scattered embryonic cells with relatively small nuclei. These morphological aspects are not at all specific to *T. canis* larvae, as they are similar to other nematode larvae, such as *S. stercoralis*.

In toxocariasis, eosinophilia can reach 70% in either blood or CSF (90). It is possible to have peripheral eosinophilia without CSF eosinophilia, and vice versa. CSF protein is slightly elevated in about half of toxocariasis patients, and glucose levels are usually normal (90, 176).

Immunological methods detecting the L2 excretory-secretory (TES) antigens of *T. canis* are widely recognized diagnosis tools for toxocariasis. These tests have a high sensitivity and specificity (74). Before the era of purified TES components, the preabsorption of serum samples with antigen of *Ascaris suum* was a successful strategy for improving specificity, since cross-reactivity complicates a distinct immunological diagnosis (132, 239, 240).

Recombinant proteins, like TES arginine kinase (30 kDa and 120 kDa), have been evaluated as targets for antibody detection methods (Table 7), and IgG2, IgG4, and IgE responses were found to be more specific with this method (175, 205, 294). The adsorption of recombinant antigens into polysiloxane-polyvinyl alcohol beads has also been reported as a more sensitive method than classical ELISA (60). There are autoantibodies against small nuclear ribonucleoproteins associated with toxocariasis that may recognize epitopes shared by the host and *Toxocara*. Their role in pathogenesis is unknown, and their usefulness in diagnosis is open for investigation (210).

Examination of serum samples is worthwhile in CNS toxocariasis, since negative blood and positive CSF is an exception (90). Higher antibody titers in CSF than in serum appear to be the rule, with the more frequent myelitic form in toxocariasis (112, 290). However, serum reactivity is not a reliable indicator of CNS disease activity, since serum reactivity persists long after clinical recovery (289).

Nucleic acid detection methods for diagnosis of toxocariasis are also under investigation. Analysis of sequences in the internal transcribed spacers (ITS-1 and ITS-2) of nuclear ribosomal DNA may prove useful for identifying species of *Toxocara* (166).

Treatment

There has been no clinical trial evaluating drug treatment for CNS toxocariasis. Considering that albendazole has good penetration in nervous tissues and is apparently less toxic than other anthelmintics, it remains the recommended treatment, at 5 to 15 mg/kg b.i.d. for 2 to 4 weeks (90). If immune vasculitis aggravates the clinical course of neurotoxocariasis, corticoids may be of help, but this condition is considered very rare and is also very difficult to identify (265). Overall, there is no consensus on the use of corticoids for toxocariasis.

The impact of toxocariasis can be long-term. Sequelae ensue in approximately 30% of patients, and these include persistence of cognitive deficits and weakness in the extremities.

Mortality occurs primarily in children less than 6 years old (90, 196). Experimental toxocariasis infections in mice have shown several alterations in brain lesion biomarkers that suggest progression toward chronic neurodegenerative disorders (168). This is yet another justification for multicentric studies of treatment evaluation and long-term follow-up of toxocariasis infections.

BAYLISASCARIASIS

The Parasite

The superfamily Ascaridoidea includes large cylindrical worms that live within the lumen of the intestines. These animals produce thick-walled eggs that spend some time in the environment before becoming infective. One of the most prevalent enteroparasites in humans is *Ascaris lumbricoides*. Another ascarid worm is *Baylisascaris procyonis*, which infects raccoons (*Procyon lotor*) and produces VLM in humans. Although *P. lotor* is native to North America, these animals and *B. procyonis* have been introduced worldwide (108).

History

B. procyonis was first found in raccoons in the New York Zoological Park in 1931. The genus *Baylisascaris* was established by Sprent in 1968. It is considered to be the most important cause of VLM in over 100 species of birds and mammals (108). The first human cases were reported in the mid-1980s. Human disease is rare and always entails sequelae or death.

Life Cycle and the CNS

The adult worms of *B. procyonis* live in the lumen of the small intestine and excrete thick-walled eggs that are released in feces. These eggs can remain in soil for several weeks before they embryonate and become infective. Raccoons ingest the eggs, and then the larvae hatch and enter the wall of the raccoon small intestine. There, they develop into adult worms, which return to the lumen of the intestine. When *B. procyonis* larvae are ingested by less adapted hosts, like humans and many other vertebrate species, they migrate out of the intestine and can remain encapsulated in tissues or invade the CNS and produce disease. Between 5 and 7% of the larvae are estimated to migrate into the CNS. Encapsulated larvae can be at an infective stage when a raccoon eats another host. Infection in raccoons is highly prevalent, being estimated at 70% in adults and 90% in young (108, 266).

Epidemiology

The first report of a human infection with *B. procyonis* in 1984 reflected the increasingly shared environment of raccoons and humans. A 10-month-old infant died from severe eosinophilic encephalitis, and the source of infection was likely the raccoon nest in unused chimneys of a house. Raccoons do not require a rural or sylvatic environment and, like many other wild species in recent decades, are living in urban areas. As *B. procyonis* is highly prevalent among raccoons, a huge number of eggs are released daily in feces. These eggs in the environment are extremely resistant to adverse conditions in soil, and a very low number is required to produce infection and disease. Male children are prevalent among reported cases of *B. procyonis* infection, which has been attributed to their more frequent engagement in exploratory outdoor activities (266). However, changes in the behavior of both raccoons and girls may alter this observed prevalence, so this alternate etiological pairing should not be ignored. Domestic dogs and puppies have been found to be infected with *B. procyonis*. Infected pets represent a possible great risk of infection, particularly for children (266).

Disease

Infection with *B. procyonis* is known as baylisascariasis. The systemic erratic migration of *B. procyonis* larvae may be asymptomatic or may produce visceral, cutaneous, or ocular larva migrans syndrome. The larvae may reach 1,900 μm in length and 80 μm in maximal diameter, producing extensive tissue damage (108). A macular rash on the face and trunk has been described as a manifestation of CLM produced by *B. procyonis* larvae (67, 103).

Unlike angiostrongyliasis and gnathostomiasis, ocular disease is concomitant with neurological disease in many patients. CNS disease is usually very severe and leads to sequelae or death. The typical clinical presentation of CNS disease is an acute and rapidly progressing meningoencephalitis, characterized by lethargy, ataxia, and paralysis. Fever is usually not prominent, and there is impairment of humor and consciousness. Extensor posturing, spasticity, paresis, cranial nerve involvement, ataxia, and seizures are among the neurological clinical manifestations. A less acute disease is expected in adult patients (108).

Diagnosis

CNS imaging is somewhat informative. MRI eventually demonstrates nonspecific diffuse white matter lesions. Hydrocephalus and edema are also apparent at imaging, if not before. There is no meningeal or parenchymal enhancement (67, 108, 109).

Eosinophilia in the CSF may be extremely high. It varies from 4 to 68% in mild pleocytosis to between 1 and 125 cells/mm^3. CSF eosinophilia can be present without major abnormalities in protein and glucose concentrations. Elevation of white cell counts in peripheral blood is mild, but blood eosinophilia can vary widely, from 5 to 45% (108). The diagnosis of baylisascariasis should be considered whenever eosinophilic meningoencephalitis occurs in a epidemiologically compatible setting.

As with the other tissue-dwelling parasites mentioned above, histological sectioning of infected tissue does not always reveal the infecting organism. But when detected in transverse section, *B. procyonis* has prominent lateral cuticular alae, large triangular excretory columns, and a diameter of 60 to 80 μm (243). Larvae may be isolated or amid a host inflammatory reaction of infiltrating eosinophils, histiocytes, and lymphocytes (Table 2). Large numbers of eosinophils may be found next to necrotic migration tracks and blood vessels (103, 116, 126). In patients with a less fulminant and subacute disease

course, fully developed granulomas with scattered eosinophils may be detected (126).

There are a variety of effective immunological detection methods. Antibodies can be detected in serum and CSF, preferably by ELISA but also by WB and immunofluorescence on sections of frozen L3 larvae (108). The small number of confirmed infections prevents a more extensive evaluation of sensitivity and specificity. These methods are apparently quite sensitive, since patients with clinical disease usually have positive immunological tests in both serum and CSF. Brain biopsy or autopsy material has confirmed the serum and CSF immunological diagnosis in many patients (103, 108, 126). Excretory-secretory antigens have been used as antigens in ELISA and WB, and the fraction of 33 to 45 kDa appears to be a good target for the specific detection of anti-*Baylisascaris* antibodies (28). There are cross-reactive epitopes in *B. procyonis* antigens and other parasites, but the use of selected antigenic fractions results in improved immunological diagnosis (28, 27).

Treatment

Anthelmintic drugs have not a proven beneficial for the treatment of baylisascariasis, since they lack larvicidal effects in human tissues (108). In experimental animal infections with *B. procyonis*, reduction of CNS lesions was obtained with albendazole, diethylcarbazine, mebendazole, and thiabendazole, but only when they were administered from day 1 to day 10 after the infection. Even so, albendazole (20 to 40 mg/kg/day for 1 to 4 weeks) has been used to treat most of the recently reported cases (108). Corticosteroids have been used in the majority of patients to reduce inflammatory reactions, but well-controlled studies are necessary to establish their role in treatment.

Given the severity of the disease, its poor prognosis, and the demonstrated effect of anthelmintics to prevent disease, it is prudent to immediately start prophylactic treatment with albendazole (20 to 40 mg/kg/day) or thiabendazole (50 mg/kg/day) immediately after exposure to raccoon latrines or cages. For effective prophylaxis, administration of anthelmintics should continue until epidemiological investigation has clearly excluded the possibility of *B. procyonis* eggs at the exposure site. Otherwise, treatment should be maintained for at least for 10 days. This recommendation is based on experimental infections wherein success was achieved only with treatment periods that covered expected CNS vulnerability to larval invasion (108).

PARAGONIMIASIS

The Parasite

Flukes are flatworms from the class Trematoda that are elongated, leaf-shaped, hermaphroditic organisms. Different species dwell in the lung (e.g., *Paragonimus* species), in the liver (e.g., *Fasciola hepatica*), in the intestines (e.g., *Metagonimus yokogawai*), and in the blood vessels (e.g., *Schistosoma* species). *Paragonimus* belongs to the superfamily Troglotrematoidea, and at least eight species of *Paragonimus* are known to cause human disease: *P. miyazakii*, *P. skrjabini*, *P. heterotremus*, *P. africanus*, *P. uterobilateralis*, *P. kellicoti*, *P. mexicanus*, and the most common, *P. westermani* (22, 23).

History

Similar to *Gnathostoma*, *P. westermani* was first identified in a tiger at a zoo. *P. westermani* parasites were recovered from a Bengal tiger at the Amsterdam Zoo in 1877. Consequently, the species was named after the tiger keeper, Mr. Westerman. The genus *Paragonimus* was established by Diesing in 1850, while working in Brazil. The first human infection was documented in 1879, in Taiwan (129).

Life Cycle and the CNS

Multiple mammals can be infected with adult flukes, including domestic cats and dogs. The flukes live in mammal lungs and produce eggs that pass into bronchial secretions and are eliminated via expectoration or swallowing and eventual inclusion in feces. Ultimately these eggs reach environmental freshwater. After 2 weeks of embryonation, the eggs hatch and release the free swimming miracidia. These ciliated larvae must infect mollusks for the development of cercariae. Crustaceans, such as crabs or crayfishes, may be infected by direct penetration of cercariae or by ingestion of mollusks. In these second intermediate hosts, the cercariae encyst and become metacercariae.

Ingestion of raw or undercooked crustaceans is the main mode of human infection, which results in paragonimiasis. Larvae penetrate the intestinal wall and migrate in the abdominal tissues, through the diaphragm to the lung, where they develop into adult worms (170). Eventual CNS infection occurs when flukes enter the cranial cavity through the jugular or carotid foramen and usually invade the temporal and occipital lobes of the brain (50).

Epidemiology

Paragonimus is responsible for 3.5% of food-borne parasitic CNS infections in China (310), where 290 million are estimated to be infected (170). It is endemic to several countries in South America, Africa, and particularly Asia. The distribution of the human infection is determined by dietary choices, since *Paragonimus* is acquired by ingestion of raw or undercooked crustaceans. Similar to other helminths that cause eosinophilia, *Paragonimus* has shown increased global prevalence as the breadth of human travel and food exchange expands.

Disease

Paragonimiasis manifests as a pulmonary infection, with cough, thoracic pain, and bloody sputum, but meningitis is usually not concomitant with these acute pulmonary infections (211); however, CNS infection is the most common (50%) nonpulmonary form of paragonimiasis (170, 277). Clinical manifestations of cerebral disease are, in order of decreasing frequency, seizures, focal signs, and meningismus (170). Unlike what is seen in tuberculous meningitis and other etiologies, there is no severe compromise of general condition or mental status (211). Paravertebral pain, urinary dysfunction, abnormal tendon reflexes, paresis, and muscular spasms can reflect spinal involvement (170).

From autopsy analysis and biopsies, it has been determined that the pathology of CNS paragonimiasis may affect the me-

ninges in the first exudative stage, when eosinophils may be present. Meningitis is secondary to parenchymal lesions, which progress chronically to granulomatous and fibrotic lesions (211, 212). Eggs may be found in histological sections at the border of necrotic nodules (141).

Diagnosis

CNS paragonimiasis can be difficult to detect. CSF eosinophilia is not present in all paragonimiasis patients. Thus, differentiation from tuberculous meningitis is mandatory. Other bacterial etiologies should also be considered, since CSF glucose levels are typically low (212). Cerebral involvement may include chronic silent lesions, detectable with image examination as multiple conglomerated iso-intensity or low-signal-intensity round nodules, with peripheral rim enhancement (39, 50, 141, 277). Skin tests, CFA, immunodiffusion, hemagglutination, and other techniques have been used for anti-*Paragonimus* antibody detection, with variable results (49).

Immunofluorescence, ELISA, and WB are the main methods for diagnosis (49, 170). The use of antigenic fractions and development of methods at the class or isotype level may result in improved immunological diagnosis. Proteins from adult worms (32 and 35 kDa) and egg extracts (28, 46, and 94 kDa) were recognized by WB in 98% of samples from infected patients, with 100% specificity (149). A recombinant egg antigen was evaluated by ELISA, with 90% sensitivity and 100% specificity (163).

In pulmonary and skin paragonimiasis, the definitive diagnosis is the identification of operculated eggs or the worms in sputum and biopsy specimens (Table 2). Detection of eggs in CSF should not to be expected, since most of the CNS lesions occur in the parenchyma, and meningitis is a secondary event (211).

Treatment

PZQ is 80 to 90% effective for elimination of the lung fluke. The recommended treatment is a total dose of 150 mg/kg, divided into three doses over 2 days. Triclabendazole is an alternative treatment, at 10 mg/kg/day for 3 days. Less effective are mebendazole and bithionol, which result in cure rates lower than 70% and have many side effects. Surgical removal of cerebral or spinal nodules may be necessary to relieve life-threatening mass compression effects (170).

OTHER INFECTIOUS AGENTS LESS COMMONLY CAUSING EOSINOPHILIC MENINGOENCEPHALITIS

Trichinellosis

Larval stages of nematodes from *Trichinella* species migrate and encyst in tissues of several animals, including humans (34, 86). Up to 17% of patients infected with *Trichinella spiralis* may present with neurological symptoms among a range of manifestations caused by the disseminated migration of larvae. Only very few patients show predominantly neurological effects, and CSF eosinophilia is rare among those cases (105, 173). Headache, deep-tendon abnormal reflexes, neck stiffness, and behavior disturbances may last for a week or two, and recovery is usually spontaneous and complete. An important symptom cluster for diagnosis is the combination of swelling facial lesions on the lids or the lips, an acute fever, and myalgias.

Trichinella infection is most commonly acquired by consumption of inadequately cooked pork from domestic pigs. Undercooked meat from walrus, bear, cougar, and wild boar can also be a source of trichinellosis (173, 185). The main diagnostic criterion for trichinellosis is a history of eating undercooked meat, especially pork products, together with the clinical detection of blood eosinophilia. CSF is normal in most patients (173). Antibodies are detected by serology, with either ELISA or WB (308). The study of trichinellosis in animals has led to some well-defined and cloned molecules that may improve antibody detection methods in humans (29, 200). At the onset of the clinical course, weak humoral reactivity may lead to false-negative results in immunological tests (199). Multiplex PCR can detect *Trichinella* DNA and differentiate it from that of several other organisms, but a negative result from a muscle sample does not exclude the possibility of CNS infection (173, 312). A muscle biopsy that reveals encysted larvae will confirm the diagnosis (34) (Table 2). In more severe cases, corticoids must be given, and anthelmintics are recommended. Mebendazole can be given at 200 mg/day for 5 days, or albendazole can be given at 400 mg/day for 3 days, but most *Trichinella* infections are uncomplicated and self-limited, and specific therapy is usually not required (34).

Hydatidosis

Hydatidosis is the infection with larval stage tapeworms of the genus *Echinococcus*. While the species *E. granulosus* and *E. multilocularis* are known to infect the human CNS, *E. vogeli* and *E. oligarthus* do not usually affect human nervous tissues (59). The most common cause of human hydatidosis is *E. granulosus*. Dogs are the initial host for the worm, and eggs are released with feces. After ingestion of eggs, the oncospheres are released in the upper small intestine, where they penetrate the intestinal wall and migrate through the blood or lymph stream to several tissues. Typical locations of hydatid cysts are the liver and lungs. Less common are cysts in the CNS, which occur in 2 to 8% of patients (59). All hydatid cysts grow slowly, and depending on their location can cause a variety of effects, such as headache, nausea, vomiting, weakness in the extremities, seizures, visual disturbances, and cranial nerve disturbance (286). A neurogenic bladder may result from a cyst located in the spine (82). One-third of all hydatid cysts are asymptomatic. Cysts in the CNS are usually solitary and have an intraparenchymal and supratentorial location. CNS cysts do not typically elicit a strong inflammatory reaction, even when they are in the subarachnoid space (21) (Table 2). Eosinophilic meningitis may occur as a complication of surgical resection, but this is rare (26). The cysts are seen upon tomography and MRI, and they can be differentiated from cysticerci by the absence of a solitary and visible protoscolex. By contrast, cysticerci are rarely larger than 1 cm and may be present in higher numbers in several other locations. Peripheral edema and homogeneous calcifications are rare. Antibodies can be detected with indirect hemagglutination, indirect fluorescence tests, and ELISA. Recommended treatment combines the long-term administration of albendazole or mebendazole and surgical procedures. Typical surgical interventions include the PAIR tech-

nique (puncture, aspiration of fluid, injection of 15% saline solution, and reaspiration) and complete surgical resection of the cyst (285).

Coenurosis

Coenurosis is infection with larval stages of *Taenia multiceps*, a cestode that is parasitic in canids. Cysts are larger than cysticerci (4 to 5 cm in diameter) and have multiple invaginated scolices (Table 2). CNS disease following *Taenia multiceps* infection is very rare and manifests as increased intracranial pressure. CSF eosinophilia is not the rule (19, 130).

Strongyloidiasis

Strongyloides stercoralis is an intestinal nematode of humans. Infective larvae penetrate the skin or mucosa, migrate to the lungs, and reach the gut lumen after crawling up on the surface of the bronchial tree. Intestinal strongyloidiasis is usually asymptomatic, but severe disease is associated with immunosuppressive conditions (143). Disseminated strongyloidiasis is characterized by the widespread migration of larvae (Table 2). The huge number of larvae entering the intestinal mucosa and circulating systemically increases the likelihood of CNS invasion and secondary bacterial meningitis. Enteric gram-negative bacteria gain access to the circulatory system together with the larvae as they penetrate the mucosa. Larvae may be found in CSF or CNS tissues, but eosinophilic meningitis does not occur (143, 215, 263).

Filariasis

Filarial nematodes are the major group of tissue-dwelling worms infecting humans. Filariasis is one of the most prevalent helminthic infections worldwide. The larvae of filarial parasites have been identified in CNS tissue and CSF and include *Loa loa*, *Wuchereria bancrofti*, and *Onchocerca volvulus* (Table 2). Another filarial parasite, *Meningonema peruzzii*, has been detected in the subarachnoid space of African primates, and their sheathed microfilariae have been detected in the CSF of human patients (214). But there are few reports of these parasites causing eosinophilic meningitis or encephalitis in humans or other animals (80, 122, 270, 288). Conflicting results come from epidemiological investigations of the association of onchocerciasis and epilepsy in Africa, yet no evidence of a connection between these conditions was found in a meta-analysis of several studies (181).

Myiasis

Myiasis is the invasion of animal tissues with larval stages of flies. The larvae, called maggots, may parasitize the skin of vertebrates and produce nodular lesions with an opening that drains a serosanguineous material. Facial lesions, especially next to the eyes and in the paranasal sinus, may result in bone erosion and migration of the larvae to the CNS, where eosinophilic meningitis may ensue. Diagnosis is clinical, and image analysis may show a migration track along with suspected larvae that vary from 2 to 30 mm in length (Table 2). The efficacy of thiabendazole or other anthelmintic therapeutics is not established, and surgical resection may be necessary (104).

Fungal Infections

Coccidioidomycosis is the most prevalent fungal cause of eosinophilic meningitis. It has a well-defined geographic distribution; it is endemic to desert areas in the southwestern United States and northwestern Mexico. Besides *Coccidioides immitis*, *Coccidioides posadasii* has been described as a new species causing coccidioidomycosis (98). First, inhalation of conidia causes a systemic mycosis. The first stage of multiplication takes place in the lungs and is followed by dissemination, which does not necessarily result in disseminated disease.

According to records from areas of endemicity in the United States, roughly 30% of patients with CNS infections caused by *C. immitis* present with significant CSF eosinophilia (i.e., more than 10% of total leukocyte counts or at least 10 eosinophils per mm^3), while another 40% of these patients have lower counts (133, 235). (The remaining 30% have no eosinophils detected.) Other reports describe eosinophilic meningitis as a very rare manifestation of *C. immitis* infection. Pleocytosis is usually modest, and lymphocytes predominate. CSF glucose levels are decreased, and protein levels are usually higher than 150 mg/dl. Fungal endosporulating spherules are seldom visualized in CSF or biopsies. Recovery of spherules may be enhanced by urine filtration (70). CSF cultures are positive for only a small number of cases (139).

Detection of IgG and IgM antibodies is best performed by immunodiffusion and CFA techniques. IgM antibodies can be detected between 1 to 3 weeks and 4 months after infection. Although positive serum CFA is considered a hallmark of disseminated disease, these antibodies are not detected in 30% of coccidioidal meningitis patients, so their absence should not rule out diagnosis (264).

Without treatment, coccidioidal meningitis is universally fatal (271). Fluconazole in high doses (up to 1,200 mg/day) is currently the best option for treatment (139). Itraconazole, voriconazole, and intrathecal amphotericin B are also options. Whatever the choice, treatment should be sustained for years, since therapy is not curative, and the fungus remains latent in tissue even after successful clinical remission (76, 271, 300).

Other mycoses that affect the CNS do not produce eosinophilic inflammatory reactions in the meninges, except for rare occasions. They are cryptococcosis, candidiasis, aspergillosis, histoplasmosis, blastomycosis, and mucormycosis (7, 19, 114).

Bacterial, Viral, and Allergic Diseases

Meningeal eosinophilic reaction may be concomitant with other infections. These include allergic aspergillus sinusitis (37), streptococcal newborn infection (190), coxsackie viral meningitis (44), and lymphocytic choriomeningitis virus (152). Also associated with CSF eosinophilia is rickettsial disease and Rocky Mountain spotted fever (63). CSF eosinophilia has been described in a few cases of neurosyphilis and tuberculous meningitis but without a well-documented etiological role for these bacteria (152). It is of historical relevance to mention that the earliest report of eosinophilic meningitis in 1907 involved a patient with neurosyphilis (152). Rheumatoid arthritis (121),

TABLE 8. Most common causes of eosinophilic meningoencephalitis, with percentages of the helminthiasis cases with CSF eosinophilia[a]

Helminthiasis	Parasite's usual habitat in humans	Total no. of infected humans	Maximum % of patients with CSF eosinophilia	Reference(s)
Angiostrongyliasis	CNS	2,827	100	230, 293
Gnathostomiasis	Skin	230	100	24, 230, 237
Cysticercosis	CNS, muscle, skin, eye	~1,000,000 (active disease; CNS and other locations)	Unknown	276
Schistosomiasis	Mesenteric veins	550	50	48, 94
Toxocariasis	Liver, eye, and several other organs	50	80	90
Baylisascariasis	CNS	20	100	108, 266
Paragonimiasis	Lung	20	80	49, 170, 211, 212

[a] Rough estimates made from data in the literature.

Behçet's disease (115), and neurosarcoidosis (254) are occasionally associated with meningeal eosinophilic infiltrates. Eosinophils were also rarely found in conjunction with cerebral ischemia and hemorrhage (25).

NEOPLASTIC DISEASES

Clonal proliferation of eosinophils and CSF eosinophilia have been documented with acute lymphoblastic leukemia and undifferentiated myeloproliferative disorders (135). This proliferation is in contrast to the list of hematological neoplasms where there is malignant proliferation of these cells, such as chronic eosinophilic leukemia, systemic mastocytosis, chronic myelomonocytic leukemia, juvenile myelomonocytic leukemia, chronic myeloid leukemia, atypical chronic myeloid leukemia, acute myeloid leukemia, myelodysplastic syndrome, and acute lymphoblastic leukemia (99). In the most common neoplasia associated with CSF eosinophilia, Hodgkin's disease, eosinophilic pleocytosis is rare (125, 219, 272).

The eosinophil morphology is usually normal, and immature eosinophils are extremely rare, even in eosinophilic leukemia (20, 53). It is important to bear in mind that clonal eosinophilia as a truly neoplastic disorder is much less frequent than eosinophilia reactive to an infection, an allergen, or a malignant cell. Reactive CSF eosinophilia has also been detected in T-lineage non-Hodgkin's lymphoma (99). Other malignancies that may involve CSF eosinophilia are disseminated glioblastoma (71) and carcinomatosis (62).

Idiopathic hypereosinophilic syndrome (IHS) is a disorder characterized by eosinophilia of unknown origin lasting longer than 6 months. The signs of IHS are cell counts exceeding 1,500/μl of blood in the absence of known causes of eosinophilia, accompanied by organ damage or dysfunction due to release of the toxic components of eosinophil granules. Although nervous tissues are reported to be affected in 54% of IHS patients, neurological disturbances and specific eosinophilic meningitis are not a common finding (296, 299). From five reports that included CSF examination, only two out of eight IHS patients had increased CSF eosinophil counts (53, 142, 155, 194, 279). In some cases, the distinction between IHS and leukemia is problematic, and infiltration of the meninges with eosinophils suggests a diagnosis of malignancy (269). Besides the classical criteria initially proposed in 1975, absence of clonality and rearrangements in genes like PDGFRA (the gene for platelet-derived growth factor receptor, alpha polypeptide), should be included in the diagnostic workup (56).

DRUGS, REAGENTS, AND PLASTIC DEVICES

CSF eosinophilia can be associated with causes other than living infectious agents. There are a few reports of CSF eosinophilia associated with use of drugs. Associations with ibuprofen (232), ciprofloxacin (10), and intraventricular vancomycin (113) and gentamicin (189) have been found. When the resolution of symptoms and disappearance of CSF eosinophils follow the discontinuation of these drugs, the association of the eosinophilic meningitis with the underlying condition requiring the drug treatment can be ruled out (232). CSF eosinophilia may indicate malfunction of a plastic implant or any nonorganic materials coming in contact with the meninges (278). Eosinophilia has also been associated with catheters impregnated with rifampin and minocycline (18). Therefore, the meningeal reaction to these drugs cannot be ruled out. CSF eosinophilia is present in up to 30% of children with an intraventricular shunt. This measurement must be taken as an indicator of treatment malfunction and/or an infectious complication (106, 283). In addition, contrast media for myelography, like iodized oil, may induce eosinophilic meningitis in some patients (124, 140, 182, 183). Detection of eosinophilic arachnoiditis in human immunodeficiency virus-negative drug addicts without evidence for other causes suggests that illicit drugs may also lead to CSF eosinophilia (242).

CONCLUDING REMARKS

Generally, eosinophilia is classified as one of the following: (i) reactive, such as in the inflammatory reaction to helminths; (ii) clonal, as in eosinophilic leukemia; or (iii) unexplained, as in IHS (99). CSF eosinophilia is most frequently associated with reaction to infectious agents.

As demonstrated by experimental animal studies of helminthic infections, the occurrence of eosinophilic meningitis is dependent on the localization of parasite structures next to the meninges (148). Cystic larval parasitic stages, in the form of hydatids, cysticerci, and coenuri, may produce endocranial hypertension. Spinal taps are usually avoided, to foster a better evaluation of meningeal reaction, if it ever occurs. Meningeal reaction occurs mainly after rupture or degradation of the cystic larvae (276). *A. cantonensis*, *T. solium* cysticerci, and *B.*

TABLE 9. Conditions less commonly associated with CSF eosinophilia

Cause of eosinophilia	Frequency of association	Reference(s)
Nematode infections (roundworms)		
Trichinellosis	Rare	105, 173
Strongyloidiasis	Exceptionally rare	143
Filariasis	Exceptionally rare	80, 288
Cestode infections (tapeworms)		
Hydatidosis (surgical complication)	Rare	26
Coenurosis	Exceptionally rare	19, 130
Arthropod infections		
Myiasis	Exceptionally rare	104
Fungal infections		
Coccidioidomycosis	70% of patients	235
Cryptococcosis	Exceptionally rare	114
Bacterial and viral infections		
Syphilis, tuberculosis, and others; Coxsackie virus, lymphocytic choriomeningitis virus, and others	Exceptionally rare; uncertain causality	152, 295
Inflammatory diseases		
Rheumatoid arthritis	Exceptionally rare	121
Behçet's disease	Exceptionally rare	115
Sarcoidosis	Exceptionally rare	254
Neoplastic diseases		
Hodgkin's lymphoma	Rare	125
Other neoplastic diseases	Exceptionally rare	62, 71, 135
Idiopathic hypereosinophilic	Rare	296, 299
Drugs, reagents, and plastic devices		
Nonsteroidal anti-inflammatory agents	Exceptionally rare	232
Antibiotics	Exceptionally rare	10, 113, 189
Myelography contrast media	Exceptionally rare	124, 140
Illicit drugs	Isolated report	242
Plastic catheters/shunts	30% of malfunctioning devices	106, 283

procyonis are truly neurotropic parasites, while other parasites in the CNS result from ectopic migration. This fact may partially explain the frequency of the several helminths causing eosinophilic meningoencephalitis (Table 8). It should be stressed that some tissue-dwelling nematodes that cause blood eosinophilia, such as *S. stercoralis* and *Trichinella* species, are not prevalent causes for eosinophilic meningoencephalitis even when they migrate to CNS (Table 9) (152).

In helminth infections that involve parasite migration to non-CNS tissues, the compromise of nervous tissues is not necessarily concomitant with lesions at other sites. For example, in meningoencephalitis produced by *G. spinigerum*, only less than 10% of patients had skin lesions (231). Another shared feature of multiple-tissue helminths is the relatively greater severity of lesions and inflammatory reactions caused by dead parasites than those caused by live ones. This is a cause of concern for the use of anthelmintic drugs and emphasizes the need to use corticoids (90, 94, 249, 276).

Parasites infecting the CNS are rarely seen in CSF, which makes a definitive parasitological diagnosis elusive. For the same reason, the standardization of immunological methods is weakened by a lack of extensive evaluation of sensitivity and specificity. Thus, serology is the strongest source of information for strengthening the etiological hypothesis. This concept is unfortunately not clear to many researchers and physicians, as demonstrated by equivocal statements that a given serological method was "able to specifically confirm a presumptive diagnosis." Detection of antibodies will never be confirmatory, but it may certainly give strong support to the etiological hypothesis. An active search for useful panels of well-defined and purified antigens, preferably recombinant molecules, is urgently needed. Also urgent is the need for standardization of nucleic acid detection methods that can be applied to CSF samples, for better detection of meningoencephalitis. There is an ongoing effort to establish a worldwide multicenter laboratory network for evaluation and quality control of diagnostic methods for helminthic causes of eosinophilic meningoencephalitis. Physicians should contact local public health services for updated information on sources for diagnostic tests.

The permeability of geographic boundaries, facility of travel, increase in migrating populations, and various globalization phenomena have increased the movement of people and the transport of "exotic" foods. Due to this movement, so-called negative epidemiological indicators do not strongly influence the etiological consideration of infectious diseases as they have had in the past. Food safety is a legitimate concern everywhere, especially for the two main causes of eosinophilic meningoencephalitis: angiostrongyliasis and gnathostomiasis. Increased introduction of hosts to new settings and climate change may create the opportunity for geographic spread of parasites.

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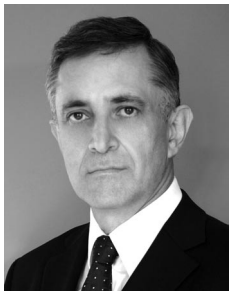

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