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Do Helminths cause Epilepsy?

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Abstract

Both helminthiases and epilepsy occur globally, and are particularly prevalent in developing regions of the world. Studies have suggested an association between epilepsy and helminth infection, but a causal relationship is not established in many helminths, except perhaps with neurocysticercosis. We review the available literature on the global burden of helminths, and the epidemiological evidence linking helminths to epilepsy. We discuss possible routes that helminths affect the central nervous system of humans and the immunological response to helminth infection in the central nervous system, looking at possible mechanisms of epileptogenesis. Finally, we discuss the current gaps in knowledge about the interaction between helminths and epilepsy.

Keywords

helminths; epilepsy; seizures; burden; pathogenesis

INTRODUCTION

Epilepsy and helminths occur throughout the world, with the prevalence higher in poor countries, particularly those in tropical regions. Helminths are parasitic worms, some of which infest humans, and even a smaller proportion is associated with neurological conditions, such as epilepsy. The importance of these organisms as a cause of epilepsy is that they can be eradicated, and thus the burden of epilepsy may be significantly reduced. In this review, we examine the possible association between helminth infection and epilepsy, the pathogenesis of epilepsy in helminth infections, and estimate the possible burden of epilepsy attributable to helminth infections. We do not discuss clinical presentation or treatment of these infections, as these aspects have been reviewed recently[1].

METHODS

We reviewed the literature detected by a search of PubMed for papers from 1966 to 13th November 2008, including electronic early release publications. We only included papers in

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English and French, the languages understood by the authors. The search terms and results of the search are outlined in Table 1.

HELMINTHS

Global Burden of Helminths causing neurological disease

Helminths can be divided into the two major phyla, namely the nematodes (which include soil transmitted helminths and filarial species) and platyhelminths (flukes and tapeworms) (Table 2). The distribution of helminth infections is heterogeneous and estimates show that developing regions of the world have the highest prevalence of helminthiases. It is suggested that 2.2 billion people are infected with a helminth, with the poorest bearing the brunt of the burden, particularly school-aged children for undetermined reasons[2]. Most people harbour these worms without overt symptoms, but it is increasingly recognised that many of these worms cause subtle effects such as stunting, reduced physical fitness, and central nervous system (CNS) involvement such as impaired memory and cognition[3].

Only a few helminths cause CNS manifestations (Table 2), some cause seizures[1], but fewer are associated with epilepsy. Neurocysticercosis, caused by *T. solium*, is the best documented, since it appears to be an important cause of epilepsy in South and Central America, where it is estimated to account for 30% of seizures in some areas[4]. The relationship between epilepsy and the other helminths is less clear.

Immunology of Helminthiases

Helminths, with the exception of Strongloides species, do not replicate in humans, rather humans act either as the definitive host (e.g. *Taenia species, Schistosoma sp.*) in which the adult worms produce eggs, with replication outside the human or as accidental intermediate hosts (*Toxocara sp.*). However, in most species the human CNS disease occurs when the human acts as an intermediate host; in which the larval stages are associated with the CNS pathology, whilst the adult worms are rarely involved.

Helminths induce both humeral and cellular responses, resulting in a delicate balance between an immunological T-cell helper-1 (Th1) and Th2 response during the infection. Although Th1 responses are thought to be responsible for parasite destruction, the Th2 response is the predominant response, involved in an immunological cascade with increases in interleukins (IL) such as IL-4, IL-5, IL-9, IL-10 and IL-13, induction of immunoglobulin E (IgE), activation of eosinophils and mast cells, producing pathological changes[5]. In particular, the Th2 response mediates the initial granulomatous formation, characteristic of many chronic parasitic infections of the brain, and thus the Th2 response is thought to play a role in epileptogenesis.[6]

Animal models of helminth infections of the brain

There are few animal models of helminth infections of the brain, particularly those that can be used to study epileptogenesis. *Taenia crassiceps* produces cysticerci in the peritoneum of mice that resemble granulomas found in human neurocysticercosis [7]. Extracts from the murine granulomas caused by *T. crassiceps cysticercia* precipitate seizures when injected into the hippocampus of rats, but homogenates of this parasite did not[8]. Interestingly, it was the extracts from the early stage granulomas, but not the older granulomas that appeared most epileptogenic, suggesting that it is the early inflammatory response to the dying parasite that is responsible for epileptogenesis. The putative substances are yet to be identified, but are likely to contain proteases[9].

Further work with *T. crassiceps cysticercia* demonstrates that the Th2 response, with subsequent production of IL-4 acts in a protective manner, preventing inflammation while simultaneously isolating the cyst[6], similar to that seen in schistosomiasis[10]. Brunet *et al.* have shown that IL-4 deficient mice are incapable of a Th2 response to the parasite[11]. However, inhibition of the Th2 response causes severe inflammation and associated morbidity; whereas, suppression of the Th1 response can cause severe fibrosis.

Immunological evidence in humans

Studies have found raised soluble IL-2 levels in cerebrospinal fluid in symptomatic patients, suggesting a Th1response[12]. More recent studies have shown elevated levels of IL-5[13,14,14], IL-6[15] and IL-10[14] cytokines in patients with active neurocysticercosis, supporting Th2 mediated response as a causes of symptomatic disease. In addition there is evidence from humans that eosionophils are important in the inflammatory response with increased levels of IL-5 and eotaxin[16]. Astrocytes appear to be an important source of chemokines following larval antigen stimulation, since *ex vivo* demonstrate are nuclear factor-B dependent, involving activator protein-1, and monocyte-derived tumour necrosis factor[17].

EPILEPSY

Epilepsy has been defined as a condition characterized by recurrent (two or more) unprovoked epileptic seizures, occurring at least 24 hours apart[18]. The seizures are caused by an abnormal electrical discharge, mainly within the cortex (gray matter) of the brain. All humans have the potential to develop seizures, but the threshold for seizures (most probably determined by the human's genome) varies considerably between individuals. Seizures are often provoked by acute infections of the CNS, so called acute symptomatic seizures, but these types of seizures do not fulfill the international definitions of epilepsy[19]. Epilepsy may develop later in response to the chronic pathological changes, or other mechanisms discussed below.

The seizures are classified as generalized or partial, depending on site within the brain where the discharge occurs[19]. The discharges can be detected by electroencephalography, but more often, the seizures are classified according to their clinical characteristics (semiology). The discharge may start in one part of the brain, spreading to other parts and thus become generalized (partial becoming generalized seizures). Most seizures, and nearly all generalized seizures, are characterized with a loss of consciousness. Epilepsy is often classified as syndromes[20], but few of these are associated with parasitic disease[21]. Although brain insults such as granulomas cause localized discharges, these discharges are often not detected as focal seizures since the secondary generalization occurs rapidly, so that the history of the seizures does not provide sufficient information to identify these as partial seizures.

Epilepsy has many different causes, including specific genes, head trauma, tumors and infections. However in most patients with epilepsy the cause cannot be determined, and thus it is termed idiopathic[19]. The proportion of patients with idiopathic epilepsy is determined by the facilities available to investigate the causes, particularly neuroimaging. In poor countries these facilities are often limited, and a greater proportion of epilepsy is labeled idiopathic than in the West.

The World Health Organization estimates that epilepsy represents 0.5% of the global burden of disease, affecting over 50 million people, of whom 80% live in poor countries[22]. The incidence and prevalence are thought to be much greater in the poorer areas of the world than the high-income countries. Thus in Africa the median prevalence is 5-74/1000[23], whilst in South America the range is 6-43/1000[4,24], and in Asia it is 2-14/1000[25] compared to

3-8/1000 in Europe[26]. The incidence is thought to be even higher, up to five times that of the West, although there are fewer studies on which to base this estimate.

The higher prevalence and incidence of epilepsy in poorer countries is attributed to a greater incidence of focal brain insults, in particular trauma and infections. Infections of the brain associated with the development of epilepsy e.g. bacterial meningitis[27] are more common in these regions, However the most commonly recognized infections do not account for the increase in epilepsy in these regions. Thus, other more subtle causes, including helminths, may contribute to the increased prevalence of epilepsy in these areas.

Difficulties in establishing the link between helminths and epilepsy

In endemic areas, much of the population harbour helminths or have serological evidence of exposure to helminths, yet are without symptoms. Thus attribution of a condition such as epilepsy, to the worm infestation is problematic; particularly as there are many causes of epilepsy (most of which cannot be excluded in endemic areas), and much of epilepsy is idiopathic. Furthermore, treatment of the helminth infections may not cure the epilepsy[28], since the parasite causes a focal lesion or inflammatory reaction in the brain that persists or becomes calcified. As a result, case reports attributing epilepsy to the presence of the worms need to be interpretated with caution. Even in the context of neurocysticersosis, where cysticerci can be easily detected by neuroimaging, attributing the cause of epilepsy is problematic. For example 14% people living in endemic area for cysticercosis in Peru without a history of seizures or other neurological signs had evidence of neurocysticercosis on computerised tomographic scans[29].

Properly conducted epidemiological studies, particularly case control studies provide the most reliable evidence of an association between the presence or exposure to helminths and epilepsy. This does not necessarily imply causation, since other factors such as poor access to health facilities and conditions associated with poverty may be common to both conditions. It is likely that a causal relationship can be established only by measuring the reduction in the incidence of epilepsy following the eradication of the putative helminth.

Epidemiological evidence—Most of the epidemiological evidence for the association between epilepsy and helminths comes from case control studies. Thus there is compelling evidence that cysticercosis is associated with epilepsy in Africa[30,31], Asia[32] and particularly South and Central America[33-38], where cysticercosis is thought to cause 25-30% of cases of epilepsy in endemic areas[29]. However there is a lack of longitudinal studies to examine the incidence of epilepsy following infection[39], or a reduction in epilepsy following control of cysticercosis. Furthermore the variable response to treatment has complicated the interpretation of these data[28].

There is less data about the association between toxocara species and epilepsy. Most of the studies describe a significant association in Italy[40,41], the United States[42,43], Bolivia[38] Burundi[44] and Tanzania[45-47]; but a study in Turkey[42], where the prevalence of toxocara is high[48], did not find an association, although there were only 100 cases and 50 controls. One consideration is the type of epilepsy examined in the studies, since the strongest associations have been found with focal epilepsies[44], and thus case control studies may not detect an association if they include predominately generalised epilepsies.

The association between onchocerciasis and epilepsy is even more controversial. A significant association was found in Burundi[49], Uganda[50,51] and Tanzania[52], but not in West or Central Africa[52]. A meta-analysis found the association to be of borderline significance [relative risk 1.21(95% CI 0.99-1.47; p = 0.06)], and was not able to find any relationship with endemicity[52]. Differences in the strains of the *Onchocerca volvulus* between East

Africa and other parts of Africa may explain the inconsistencies. Other factors such as differences in the host and the presence of mass treatment programme in some areas, may also effect the studies. More recently, a significant proportion of the subcutaneous nodules found in patients living an Ugandan area with onchocerciasis, were caused by *Taenia solium*; questioning the attribution of epilepsy to onchocerciasis in areas where both conditions occur[53]. However, there is a report that the seizure frequency is reduced following mass ivermectin treatment for onchocerciasis in an endemic area in Uganda[54], but it is unclear if this reduction is sustained, translates into a reduction in epilepsy, or is caused by possible anti-epileptic properties of ivermectin itself[55].

Of the other helminth infections, there is only one study reporting an association between exposure to spirometral infections (as detected by Ig G antibodies) and epilepsy, in which 2.5% of Korean patients with epilepsy had antibodies compared to 1.9% controls[56]. There are no case control studies demonstrating an association between epilepsy to schistosomiasis, paragonimiasis, echinococcus or the other helminths. The link between epilepsy to these helminths has come from case reports or case series, although one series of 250 cases of *S. japonicum* associated with epilepsy is compelling[57]. The seizures reported in these infections often occur during the acute infections of the brain (acute symptomatic seizures) and have not been reported to be associated with chronic epilepsy.

Many of the case control studies that report an association are retrospective studies using prevalent cases, and thus may have selection bias. Furthermore, since helminth infections are more prevalent in populations in which other causes of epilepsy are common e.g. head trauma, spurious associations may arise and reverse causality cannot be excluded.

Entry into the brain—The larvae or ova of helminths usually reach the brain via the blood. Where the human is an accidental intermediate host e.g. *Taenia sp.*, the eggs are ingested, develop into metacestodes before becoming implanted in tissues. In the tissues they develop into cystic structures, often causing granulomatous formation (*Echinococcus sp.*) with perilesional edema (*Taenia sp.*). The appearance of symptoms depends upon the number, size, and whether the cyst is active or inactive. Other features such as the localization of the cyst(s), compression of the surrounding tissues by the cyst and inflammatory response of the infected individual also contribute to the symptomatology.

In other species, the eggs hatch in the intestine, producing larvae that penetrate the intestinal wall, before haematogenous spread to the brain. The larvae induce a granulamotous reaction (e.g. Toxocara), which may develop into discrete granulomas, surrounding the larvae within a cyst e.g. Trichinella. The seizures may be precipitated by the granulomatous inflammation of the brain parenchyma and/or an allergic reaction, or are secondary to haemorrhages.

The schistosoma species generally infect humans via the skin and migrate to the organs of predilection, in which the adult worms mate, producing eggs. Usually the eggs egress from the body via bladder or rectum. However, in rare instances, the eggs are transported to the brain via the iliac veins and inferior vena cava or migrate via pulmonary arteriovenous shunts or portal-pulmonary arteriovenous shunts. Very rarely, the worms will migrate to the cerebral veins, where they deposit their eggs[58]. *S. japonicum* is associated with cerebral lesions more than the other species. The eggs set up a granulomatous reaction, which eventually kills the eggs leaving a fibrotic scar.

Sparganosis and paragonimiasis are uncommon infections found mainly in Eastern Asia, with the definitive hosts as cats and dogs. These conditions are caused by *Spirometra mansoni* and *Paragonimus sp.*, respectively. They are similar in that they have two intermediate hosts, with humans infected by drinking contaminated water, eating raw

chicken or fish (sparganosis); or crabs (paragonimiasis). CNS involvement is relatively uncommon. In both infections there may be an initial meningoencephalitis, followed by the development of the granulomata. In sparganosis the granulomas often become calcified, whilst in paragonimiasis the granulomas evolve into encapsulated abscesses, developing into cystic lesions, which infrequently become calcified[59]. Seizures are common CNS manifestations of paragonimiasis, but they are usually acute symptomatic seizures, although epilepsy may develop in association with the chronic lesions[60].

Epileptogenesis of parasitic infections—The pathogenesis of epilepsy in helminth infections is unclear. As mentioned above, most helminths appear to precipitate seizures by producing focal lesions in the brain, often associated with a surrounding inflammatory reaction. These lesions may perturb the neuronal cells, giving rise to epileptic discharges in susceptible individuals. It is unclear if it is the lesion itself or the surrounding inflammation (that often occurs), that is responsible for the discharges. Furthermore, the epileptogenic potential of a lesion depends upon the site, since some parts of the brain are more susceptible to producing epileptic discharges than other parts. Other mechanisms include the direct invasion of the CNS by the worm or antibody mediated epileptogenesis.

The nature of the lesion produced by the helminth may dictate the epileptogenic potential. Acute granulomatous reactions may cause acute symptomatic seizures, and may leave fibrous scars after resolution. However some helminths e.g. toxocara or schistosomes produce chronic granulomatous lesions[61] leading to epilepsy (Figure 1). In sparganosis the characteristically few acute lesions in the brain do not appear to cause seizures, but seizures appear to be associated with chronic lesions[62].

The mechanisms by which *T. Solium* causes seizures has been the most studied, and may provide insights into the epileptogenesis of the other helminths. In neurocysticercosis the parasite appears to pass through four phases in the brain, which can be seen with neuroimaging (Figure 2), although this sequence has not been confirmed experimentally[63]. The initial vesicular phase is characterised by larva inside translucent liquid-filled cystic structures surrounded by a thin membrane. The larva can remain viable for months to years, and do not appear to elicit an immune reaction in the brain, nor appear to cause of symptoms. The cyst degenerates, passing through a transitional stage in which edema occurs around the cyst. These stages may be associated with clinical manifestations, such as seizures, but in many people this stage is asymptomatic. Thereafter the cyst dies, either disappearing or becoming an inactive calcified nodule. These calcified lesions appear to be inert, yet if occur in certain parts of the brain in a susceptible individual may produce seizures. More than one stage may appear in the same individual, complicating the investigation into the pathogenesis of epilepsy in this condition.

In the transitional stages, the seizures are thought to be caused by compression of the brain tissue, but inflammation as documented by enhancement of the effected tissue on MRI and cytokines in the cerebrospinal fluid[14] may also be important. During treatment of cysticercosis, edema often increases with deterioration in the patient's clinical state, increasing seizure frequency. This has led to the use of anti-inflammatory agents such as corticosteroids to reduce this effect. The role of anti-inflammatory agents such as corticosteroids are controversial, since no clinical trials have been reported that address this specific issue[64]. Seizures in the calcified stages are attributed to gliosis, left after the cyst has disappeared that result in chronic epileptogenic foci. Peri-lesional edema, visible on contrast-enhanced neuroimaging, can persist in the calcified stage and is associated with an increased risk of epilepsy[65]. The edema surrounding these calcified lesions may be a persistent inflammatory response provoked by antigens released from the lesions. It is not clear why only some of the calcified lesions appear to induce inflammation, but the calcified

lesions may be heterogeneous, presenting a variety of antigens or releasing different compounds into the parenchyma, and thus inducing different inflammatory responses

Other mechanisms, besides those associated with inflammation and cyst formation, for epileptogenesis in neurocysticercosis also occur. Seizures may occur in relation to cerebral infarction following vasculitis and thrombosis in subarachnoid involvement. Residual brain damage, manifesting as gliosis or encephalomalcia may also be responsible.

The cause of epilepsy in onchocerciasis is unclear. Other clinical manifestations e.g. blindness of onchocerciasis are thought to be caused by the inflammatory responses to dead or dying microfilariae (>100 000 more microfilariae die every day in a heavily infected person)[66]. The immune responses are predominantly antibody mediated, but cellular components are also important. In the eye, lymphocytes, macrophages and to a lesser extent eosinophils are present. There is activation of vascular endothelium, with pericytes and fibroblasts in persons with chronic eye changes. Down-regulation of the immune response in chronically infected eye tissue and adult worms may elaborate substances that inhibit the immune response. Although the eye is often thought to reflect the pathological processes in the brain (since these organs are derived from the same embryological tissue), there has not been evidence that these mechanisms occur in patients with epilepsy.

Other proposed mechanisms of onchocerciasis include entry of the adult worm into the CNS, and the generation of autoantibodies. There are no pathological studies that have reported adult worms within the CNS, and there are no neuroimaging studies that have demonstrated lesions associated with adult worms. Microfilaria have been seen in the cerebrospinal fluid of untreated patients with onchocerciasis[67,68] and after the onset of treatment[67], but no studies have been reported that examined the association of microfilaria in the cerebrospinal fluid with epilepsy. Autoantibodies to the retinal photoreceptors have been found in the inner retina of patients with onchocerciasis[69], but the relationship with retinal damage is not clear. There have been no reports between the presence of autoantibodies and epilepsy in onchocerciasis.

Parasites may produce substances that interfere with neuronal transmission. For example *P.westermani* and *S.mansoni* produce proteases which may cause brain damage[70]. Whether this leads to epilepsy in these infections, or whether similar mechanisms occur in other helminth infections is unknown.

Helminths generate a marked immune response, including autoantibodies[67,71-74]. There is growing evidence that autoantibodies against neuronal elements may be responsible for some epilepsy[46,75]. Specific antibodies to NMDA receptors are associated with an encephalopathy characterised by epilepsy. Antiphospholipid[45], anticardiolipin and antinuclear antibodies[45,46] are more frequent in people with epilepsy than appropriate controls. Autoantibodies against neuronal elements such as glutamate receptors, voltage gated calcium and potassium channels occur in patients with epilepsy [76]. To date, it is unclear if these immune mediated mechanisms are responsible for the epilepsy in helminth infections.

GAPS IN RESEARCH

There is considerable lack of the data in the epidemiology of the helminths associated with neurological conditions such as epilepsy. Further studies are required to assess the burden of these conditions, identify strategies to prevent transmission of these helminths, and thus reduce the burden of epilepsy. Since many helminths appear to cause seizures via inflammatory processes, the immunological basis of these infections in the brain requires further elucidation. The development of animal models may provide invaluable insights, but

more detailed human studies are clearly warranted. In particular, studies on the pathogenesis of granulomas and the mechanisms by which these lesions precipitate seizures. Work in this area may provide insights into other infectious causes of seizures and epilepsy, and basic mechanisms of epileptogenesis itself. With the advent of conditions that impair immunity, such as HIV in helminth infected regions of the globe, the immunopathology is particularly critical.

Lastly the lack of longitudinal studies makes exploring the onset of epilepsy following the initial parasitic infection has hindered the establishment of a causal link between helminths and epilepsy.

CONCLUSION

Helminths infections and epilepsy are common, particularly in the poorer areas of the world, where they can have serious consequences on the people living in those areas. The epidemiological links suggest an association, but a causal relationship is undetermined, except perhaps in the case of neurocysticercosis. The mechanisms by which helminths cause epilepsy are unclear, but immunological mechanisms are likely to be important, and may provide insights into the epileptogenesis of other conditions.

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Reference List

(1). Garcia HH, Modi M. Helminthic parasites and seizures. Epilepsia. 2008; 49:25–32. [PubMed: 18754958]

(2). Hotez PJ, Brindley PJ, Bethony JM, King CH, Pearce EJ, Jacobson J. Helminth infections: the great neglected tropical diseases. J Clin Invest. Apr; 2008 118(4):1311–21. [PubMed: 18382743]

(3). Parraga IM, Assis AM, Prado MS, et al. Gender differences in growth of school-aged children with schistosomiasis and geohelminth infection. Am J Trop Med Hyg. Aug; 1996 55(2):150–6. [PubMed: 8780452]

(4). Jallon P. Epilepsy in developing countries. Epilepsia. Oct; 1997 38(10):1143–51. [PubMed: 9579962]

(5). MacDonald AS, Araujo MI, Pearce EJ. Immunology of parasitic helminth infections. Infect Immun. Feb; 2002 70(2):427–33. [PubMed: 11796567]

(6). Robinson P, Atmar RL, Lewis DE, White AC Jr. Granuloma cytokines in murine cysticercosis. Infect Immun. Jul; 1997 65(7):2925–31. [PubMed: 9199468]

(7). Villa OF, Kuhn RE. Mice infected with the larvae of Taenia crassiceps exhibit a Th2-like immune response with concomitant anergy and downregulation of Th1-associated phenomena. Parasitology. Jun; 1996 112(Pt 6):561–70. [PubMed: 8684830]

(8). Stringer JL, Marks LM, White AC Jr. Robinson P. Epileptogenic activity of granulomas associated with murine cysticercosis. Exp Neurol. Oct; 2003 183(2):532–6. [PubMed: 14552894]

(9). Stringer JL, Marks LM, White AC Jr. Robinson P. Epileptogenic activity of granulomas associated with murine cysticercosis. Exp Neurol. Oct; 2003 183(2):532–6. [PubMed: 14552894]

(10). Pearce EJ, MacDonald AS. The immunobiology of schistosomiasis. Nat Rev Immunol. Jul; 2002 2(7):499–511. [PubMed: 12094224]

(11). Brunet LR, Sabin EA, Cheever AW, Kopf MA, Pearce EJ. Interleukin 5 (IL-5) is not required for expression of a Th2 response or host resistance mechanisms during murine schistosomiasis mansoni but does play a role in development of IL-4-producing non-T, non-B cells. Infect Immun. Jun; 1999 67(6):3014–8. [PubMed: 10338513]

(12). Rolfs A, Muhlschlegel F, Jansen-Rosseck R, et al. Clinical and immunologic follow-up study of patients with neurocysticercosis after treatment with praziquantel. Neurology. Mar; 1995 45(3 Pt 1):532–8. [PubMed: 7898711]

(13). Evans CA, Garcia HH, Hartnell A, et al. Elevated concentrations of eotaxin and interleukin-5 in human neurocysticercosis. Infect Immun. Sep; 1998 66(9):4522–5. [PubMed: 9712812]

(14). Rodrigues V Jr. de Mello FA, Magalhaes EP, Ribeiro SB, Marquez JO. Interleukin-5 and interleukin-10 are major cytokines in cerebrospinal fluid from patients with active neurocysticercosis. Braz J Med Biol Res. Sep; 2000 33(9):1059–63. [PubMed: 10973138]

(15). Evans CA, Garcia HH, Hartnell A, et al. Elevated concentrations of eotaxin and interleukin-5 in human neurocysticercosis. Infect Immun. Sep; 1998 66(9):4522–5. [PubMed: 9712812]

(16). Evans CA, Garcia HH, Hartnell A, et al. Elevated concentrations of eotaxin and interleukin-5 in human neurocysticercosis. Infect Immun. Sep; 1998 66(9):4522–5. [PubMed: 9712812]

(17). Uddin J, Garcia HH, Gilman RH, Gonzalez AE, Friedland JS. Monocyte-astrocyte networks and the regulation of chemokine secretion in neurocysticercosis. J Immunol. Sep 1; 2005 175(5): 3273–81. [PubMed: 16116219]

(18). ILAE. Guidelines for Epidemiologic studies on Epilepsy. Epilepsia. 1993; 34(4):592–6. [PubMed: 8330566]

(19). ILAE. sal for revised clinical and electroencephalographic classification of epileptic seizures. Epilepsia. 1981; 22:489–501. [PubMed: 6790275]

(20). ILAE. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia. 1989; 30(4):389–99. [PubMed: 2502382]

(21). Otero dova S, Diaz F, Garcia-Teruel I, Del Brutto OH. Acquired epileptic aphasia (the Landau-Kleffner syndrome) due to neurocysticercosis. Epilepsia. Sep; 1989 30(5):569–72. [PubMed: 2477238]

(22). WHO. The World Health Report: 2001: Mental health: new understanding, new hope. 2001

(23). Preux PM, Druet-Cabanac M. Epidemiology and aetiology of epilepsy in sub-Saharan Africa. Lancet Neurol. Jan; 2005 4(1):21–31. [PubMed: 15620854]

(24). Burneo JG, Tellez-Zenteno J, Wiebe S. Understanding the burden of epilepsy in Latin America: a systematic review of its prevalence and incidence. Epilepsy Res. Aug; 2005 66(1-3):63–74. [PubMed: 16125900]

(25). Mac TL, Tran DS, Quet F, Odermatt P, Preux PM, Tan CT. Epidemiology, aetiology, and clinical management of epilepsy in Asia: a systematic review. Lancet Neurol. Jun; 2007 6(6):533–43. [PubMed: 17509488]

(26). Forsgren L, Beghi E, Oun A, Sillanpaa M. The epidemiology of epilepsy in Europe -a systematic review. Eur J Neurol. Apr; 2005 12(4):245–53. [PubMed: 15804240]

(27). Peltola H. Burden of meningitis and other severe bacterial infections of children in africa: implications for prevention. Clin Infect Dis. Jan; 2001 32(1):64–75. [PubMed: 11112673]

(28). Del Brutto OH, Roos KL, Coffey CS, Garcia HH. Meta-analysis: Cysticidal drugs for neurocysticercosis: albendazole and praziquantel. Ann Intern Med. Jul 4; 2006 145(1):43–51. [PubMed: 16818928]

(29). Montano SM, Villaran MV, Ylquimiche L, et al. Neurocysticercosis: association between seizures, serology, and brain CT in rural Peru. Neurology. Jul 26; 2005 65(2):229–33. [PubMed: 16043791]

(30). Andriantsimahavandy A, Lesbordes JL, Rasoaharimalala B, et al. Neurocysticercosis: a major aetiological factor of late-onset epilepsy in Madagascar. Trop Med Int Health. Aug; 1997 2(8): 741–6. [PubMed: 9294543]

(31). Nsengiyumva G, Druet-Cabanac M, Ramanankandrasana B, Bouteille B, Nsizabira L, Preux PM. Cysticercosis as a major risk factor for epilepsy in Burundi, east Africa. Epilepsia. Jul; 2003 44(7):950–5. [PubMed: 12823579]

(32). Tran DS, Odermatt P, Le Oanh T, et al. Risk factors for epilepsy in rural Lao PDR: a case-control study. Southeast Asian J Trop Med Public Health. May; 2007 38(3):537–42. [PubMed: 17877231]

(33). Cruz ME, Schantz PM, Cruz I, et al. Epilepsy and neurocysticercosis in an Andean community. Int J Epidemiol. Aug; 1999 28(4):799–803. [PubMed: 10480714]

(34). Del Brutto OH, Santibanez R, Idrovo L, et al. Epilepsy and neurocysticercosis in Atahualpa: a door-to-door survey in rural coastal Ecuador. Epilepsia. Apr; 2005 46(4):583–7. [PubMed: 15816956]

(35). Gracia F, de Lao SL, Castillo L, et al. Epidemiology of epilepsy in Guaymi Indians from Bocas del Toro Province, Republic of Panama. Epilepsia. Nov; 1990 31(6):718–23. [PubMed: 2245802]

(36). Jallon P. Epidemiology of epilepsies in Latin America L'EPIDEMIOLOGIE DES EPILEPSIES EN AMERIQUE LATINE. EPILEPSIES. 1998; 10(2):123–9.

(37). Medina MT, Duron RM, Martinez L, et al. Prevalence, incidence, and etiology of epilepsies in rural Honduras: the Salama Study. Epilepsia. Jan; 2005 46(1):124–31. [PubMed: 15660778]

(38). Nicoletti A, Bartoloni A, Reggio A, et al. Epilepsy, cysticercosis, and toxocariasis: a population-based case-control study in rural Bolivia. Neurology. Apr 23; 2002 58(8):1256–61. [PubMed: 11971095]

(39). Carpio A, Escobar A, Hauser WA. Cysticercosis and epilepsy: a critical review. Epilepsia. Oct; 1998 39(10):1025–40. [PubMed: 9776322]

(40). Arpino C, Gattinara GC, Piergili D, Curatolo P. Toxocara infection and epilepsy in children: a case-control study. Epilepsia. Jan; 1990 31(1):33–6. [PubMed: 2303010]

(41). Nicoletti A, Sofia V, Mantella A, et al. Epilepsy and toxocariasis: a case-control study in Italy. Epilepsia. Apr; 2008 49(4):594–9. [PubMed: 18031545]

(42). Akyol A, Bicerol B, Ertug S, Ertabaklar H, Kiylioglu N. Epilepsy and seropositivity rates of Toxocara canis and Toxoplasma gondii. Seizure. Apr; 2007 16(3):233–7. [PubMed: 17239629]

(43). Glickman LT, Cypess RH, Crumrine PK, Gitlin DA. Toxocara infection and epilepsy in children. J Pediatr. Jan; 1979 94(1):75–8. [PubMed: 758428]

(44). Nicoletti A, Bartoloni A, Sofia V, et al. Epilepsy and toxocariasis: a case-control study in Burundi. Epilepsia. May; 2007 48(5):894–9. [PubMed: 17508999]

(45). Eriksson K, Peltola J, Keranen T, Haapala AM, Koivikko M. High prevalence of antiphospholipid antibodies in children with epilepsy: a controlled study of 50 cases. Epilepsy Res. Aug; 2001 46(2):129–37. [PubMed: 11463514]

(46). Peltola JT, Haapala A, Isojarvi JI, et al. Antiphospholipid and antinuclear antibodies in patients with epilepsy or new-onset seizure disorders. Am J Med. Dec 15; 2000 109(9):712–7. [PubMed: 11137486]

(47). Winkler AS, Blocher J, Auer H, Gotwald T, Matuja W, Schmutzhard E. Anticysticercal and antitoxocaral antibodies in people with epilepsy in rural Tanzania. Transactions of Royal Society of Tropical Medicine and Hygiene. 2008; 102(10):1032–8.

(48). Yariktas irci M, Aynali G, Kaya S, Doner F. Relationship between Toxocara seropositivity and allergic rhinitis. Am J Rhinol. Mar; 2007 21(2):248–50. [PubMed: 17424889]

(49). Newell ED, Vyungimana F, Bradley JE. Epilepsy, retarded growth and onchocerciasis, in two areas of different endemicity of onchocerciasis in Burundi. Trans R Soc Trop Med Hyg. 1997; 91(5):525–7. [PubMed: 9463656]

(50). Kipp W, Kasoro S, Burnham G. Onchocerciasis and epilepsy in Uganda. Lancet. Jan 15; 1994 343(8890):183–4. [PubMed: 7904037]

(51). Ovuga E, Kipp W, Mungherera M, Kasoro S. Epilepsy and retarded growth in a hyperendemic focus of onchocerciasis in rural western Uganda. East Afr Med J. Oct; 1992 69(10):554–6. [PubMed: 1473507]

(52). Druet-Cabanac M, Boussinesq M, Dongmo L, Farnarier G, Bouteille B, Preux PM. Review of epidemiological studies searching for a relationship between onchocerciasis and epilepsy. Neuroepidemiology. May; 2004 23(3):144–9. [PubMed: 15084784]

(53). Katabarwa M, Lakwo T, Habumogisha P, Richards F, Eberhard M. Could neurocysticercosis be the cause of "onchocerciasis-associated" epileptic seizures? Am J Trop Med Hyg. Mar; 2008 78(3):400–1. [PubMed: 18337333]

(54). Kipp W, Burnham G, Kamugisha J. Improvement in seizures after ivermectin. Lancet. Sep 26; 1992 340(8822):789–90. [PubMed: 1356196]

(55). Trailovic SM, Varagic VM. The effect of ivermectin on convulsions in rats produced by lidocaine and strychnine. Vet Res Commun. Oct; 2007 31(7):863–72. [PubMed: 17308985]

(56). Kong Y, Cho SY, Kang WS. Sparganum infections in normal adult population and epileptic patients in Korea: a seroepidemiologic observation. Kisaengchunghak Chapchi. Jun; 1994 32(2): 85–92.

(57). Lei T, Shu K, Chen X, Li L. Surgical treatment of epilepsy with chronic cerebral granuloma caused by Schistosoma japonicum. Epilepsia. Jan; 2008 49(1):73–9. [PubMed: 17662065]

(58). Preidler KW, Riepl T, Szolar D, Ranner G. Cerebral schistosomiasis: MR and CT appearance. AJNR Am J Neuroradiol. Sep; 1996 17(8):1598–600. [PubMed: 8883665]

(59). Miyazaki I. Cerebral Paragonimiasis. Contemp Neurol Ser. 1975; 12:109–32. 109-32. [PubMed: 1095292]

(60). Higashi K, Aoki H, Tatebayashi K, Morioka H, Sakata Y. Cerebral paragonimiasis. J Neurosurg. Apr; 1971 34(4):515–27. [PubMed: 4995126]

(61). Betting LE, Pirani C Jr. de Souza QL, Damasceno BP, Cendes F. Seizures and cerebral schistosomiasis. Arch Neurol. Jun; 2005 62(6):1008–10. [PubMed: 15956175]

(62). Holodniy M, Almenoff J, Loutit J, Steinberg GK. Cerebral sparganosis: case report and review. Rev Infect Dis. Jan; 1991 13(1):155–9. [PubMed: 2017616]

(63). Carpio A. Neurocysticercosis: an update. Lancet Infect Dis. Dec; 2002 2(12):751–62. [PubMed: 12467692]

(64). Nash TE, Singh G, White AC, et al. Treatment of neurocysticercosis: current status and future research needs. Neurology. Oct 10; 2006 67(7):1120–7. [PubMed: 17030744]

(65). Nash TE, Del Brutto OH, Butman JA, et al. Calcific neurocysticercosis and epileptogenesis. Neurology. Jun 8; 2004 62(11):1934–8. [PubMed: 15184592]

(66). Burnham G. Onchocerciasis. Lancet. May 2; 1998 351(9112):1341–6. [PubMed: 9643811]

(67). Marin B, Boussinesq M, Druet-Cabanac M, Kamgno J, Bouteille B, Preux PM. Onchocerciasis-related epilepsy? Prospects at a time of uncertainty. Trends Parasitol. Jan; 2006 22(1):17–20. [PubMed: 16307906]

(68). Duke BO, Vincelette J, Moore PJ. The populatin dynamics of Onchocerca volvulus microfilariae during treatment with suramin and diethylcarbamazine. Tropenmed Parasitol. Jun; 1976 27(2): 133–44. [PubMed: 941248]

(69). Chan CC, Nussenblatt RB, Kim MK, Palestine AG, Awadzi K, Ottesen EA. Immunopathology of ocular onchocerciasis. 2. Anti-retinal autoantibodies in serum and ocular fluids. Ophthalmology. Apr; 1987 94(4):439–43. [PubMed: 3295642]

(70). Lee JC, Cho GS, Kwon JH, Shin MH, Lim JH, Kim WK. Macrophageal/microglial cell activation and cerebral injury induced by excretory-secretory products secreted by Paragonimus westermani. Neurosci Res. Feb; 2006 54(2):133–9. [PubMed: 16325294]

(71). Obwaller A, Duchene M, Walochnik J, Wiedermann G, Auer H, Aspock H. Association of autoantibodies against small nuclear ribonucleoproteins (snRNPs) with symptomatic Toxocara canis infestation. Parasite Immunol. Aug; 2004 26(8-9):327–33. [PubMed: 15679629]

(72). ura-Biegun A, Pituch-Noworolska A, Rewicka M, Mrozewicz B, Noworolski J. Antistriational antibodies during Toxocara canis, Trichinella spiralis infections. Comp Immunol Microbiol Infect Dis. Apr; 1998 21(2):101–6. [PubMed: 9611680]

(73). Rahima D, Tarrab-Hazdai R, Blank M, Arnon R, Shoenfeld Y. Anti-nuclear antibodies associated with schistosomiasis and anti-schistosomal antibodies associated with SLE. Autoimmunity. 1994; 17(2):127–41. [PubMed: 8061163]

(74). Paganelli R, Ngu JL, Levinsky RJ. Circulating immune complexes in onchocerciasis. Clin Exp Immunol. Mar; 1980 39(3):570–5. [PubMed: 7379329]

(75). Levite M. Autoimmune epilepsy. Nat Immunol. Jun.2002 3(6):500. [PubMed: 12032558]

(76). Palace J, Lang B. Epilepsy: an autoimmune disease? J Neurol Neurosurg Psychiatry. Dec; 2000 69(6):711–4. [PubMed: 11080217]

(77). Hawk MW, Shahlaie K, Kim KD, Theis JH. Neurocysticercosis: a review. Surg Neurol. Feb; 2005 63(2):123–32. [PubMed: 15680651]

(78). Carod-Artal FJ. Neurological complications of Schistosoma infection. Trans R Soc Trop Med Hyg. Feb; 2008 102(2):107–16. [PubMed: 17905371]

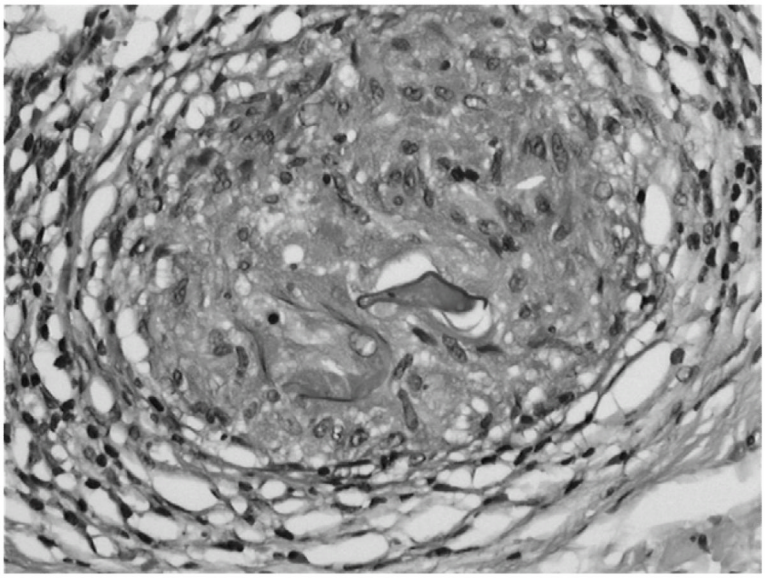

Figure 1.
Image of Schistosomia mansoni granuloma. Pathological findings from a brain biopsy. (Reprinted with permission of FJ Carod-Artal, Transactions of the Royal Society of Tropical Medicine and Hygiene (2008)[78])

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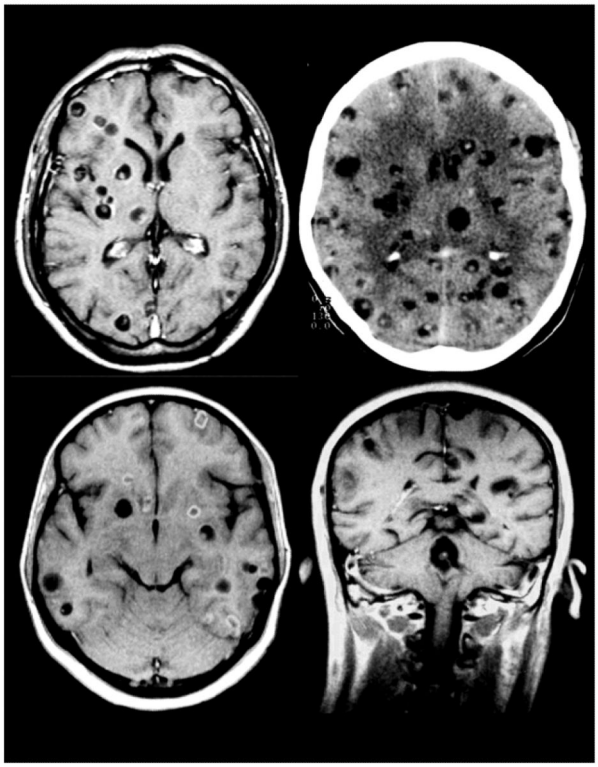

Figure 2.
Images of the different stages of the cysticerci. (A) T1-weighted MR image showing viable active cysts, some with a scolex. (B) CT scan showing calcifications and many active cysts with scolices (vesicular phase). (C) Gadolinium enhanced T1-weighted MRI of viable and transitional cysts in the colloidal and nodular-granular phases. (D) Fourth ventricle cysticercus as displayed on MRI; note a clearly defined scolex with pedicle.(Reprinted with permission of A Carpio[63])

Table 1

Literature Search Strategy and Outcome

Search Parameters	Case Studies	Series Studies	Case Control Studies	Total number of publications identified
Epilepsy AND helminths	124	20	24	370
Epilepsy OR fits OR seizures OR convulsions AND helminths	194	48	37	598
Epilepsy OR fits OR seizures OR convulsions AND cestodes	42	11	13	154
AND Cysticercosis	28	17	5	139
AND *T. solium*	0	2	1	30
AND *T. multiceps*	0	0	0	0
AND *Spriometra spp.*	0	0	0	0
AND *Echinococcus*	2	0	0	3
AND *E. granulosus*	0	0	0	0
AND *E. multilocularis*	0	0	0	0
Epilepsy OR fits OR seizures OR convulsions AND Cysticercosis	205	72	35	679
Epilepsy OR fits OR seizures OR convulsions AND Echinococcus	6	1	0	8
Epilepsy OR fits OR seizures OR convulsions AND nematodes	4	2	8	85
AND *Trichinella spiralis*	0	0	0	0
AND *Angiostrongylus cantonensis*	2	0	0	4
AND *Strongyloides stercoralis*	0	0	1	2
AND *Toxocara ca**	3	1	5	13
Epilepsy OR fits OR seizures OR convulsions AND trematodes	5	3	0	27
AND Schistosoma	4	2	0	19
AND *S. mansoni*	1	0	0	9
AND *S. haematobium*	1	0	0	3
AND S japonicum	0	1	0	5
AND Onchoceriasis	0	0	0	0
Epilepsy OR fits OR seizures OR convulsions AND Schistosoma	6	2	0	27
Epilepsy OR fits OR seizures OR convulsions AND Onchoceriasis	0	0	2	29

Table 2
Helminth Burden, Distribution, and Hosts

Worm	Global burden	Distribution	Other hosts
Cestodes (Tapeworms)			
Taenia solium, T. multiceps	Uncertain thought to >50 million[77]	Africa, Asia, South America	Pigs
Spirometra spp.	*?*	Africa	Dogs and Cats
Echinococcus (E. granulosus/ E. multilocularis)	*?*	South and Central America, Middle East, China, and western United States	Lions and Dogs
Trematodes (Flukes)			
Schistosoma (S. mansoni S. hematobium S. japonicum)	200 million[2]	Sub-Saharan Africa, South America and Asia	Snails
Paragonimus (P. westermani P. mexicanus)	>40 million[2]	East Asia, South America	Cats, snails, and crabs
Onchocerciasis	37 million[2]	Sub-Saharan Africa,	Black fly
Nematodes			
Trichinella spiralis	?	South America and Africa	Rats, pigs, foxes, and bears
(Roundworms) *Angiostrongylus cantonensis*	?	Asia and Pacific Rim	Rats, snails, slugs, and crustaceans
Strongyloides stercoralis	30-100 million[2]	Africa, Asia, South America	Dogs, cats, and primates
Toxocara (T.canis,T. catis)	*?*	Globally	Dogs and cats

? – No reliable estimate.