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Mini Review

Often Neglected Brain Lesions by Zoonotic Parasites

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Abstract

With increasing frequency and prevalence of zoonotic diseases worldwide, cases of brain lesions caused by zoonotic parasites are on the rise but often neglected. This review introduces parasitic infections that are manifested in the central nervous system, with an illustration of babesiosis in dogs, in the hope of providing understanding of these diseases before pandemic human acquisition. In such cases, pathological examination revealed most pathology in the corpus striatum, with the cortex less affected. The lesions were mostly ipsilateral and focal matching the reported circling behavior. Cytological pictures featured lymphocytes and macrophages

Keywords: Babesiosis; Encephalopathy; Nervous System; Parasitic Infection; Zoonotic Disease

Description

Parasitic infections on the nervous system of human are in fact not rare, but in the age of bacterial and viral mutations causing vigorous diseases that caught much public attention, parasitic diseases, particularly those on the nervous system, are often overlooked. Parasitic diseases that manifested in the Central Nervous System (CNS) mainly come from several large categories, many of which are transmitted via animals [1].

The first category of these parasites comes from the big category of Platyhelminthes, which includes the Cestodes (tapeworms) and the Trematodes (the flukes) [1,2]. These parasites in general can only survive inside the host. The tapeworms are segmented worms with a scolex which anchors onto the host. Infection of these parasites occurs primarily at the larval stage and rarely in the adult. One of the tapeworm species, *Taenia solium*, is well-known in inducing Neurocysticercosis (NCC) in the brain which is a relevant cause of epilepsy in endemic areas, giving rise to human morbidity and mortality [3]. The adults of tapeworm usually live in the gastrointestinal tract. Ingestion of contaminated food and the fecal-oral route are the common ways of acquiring NCC. While the most common manifestation of NCC are seizures, intracranial hypertension, and cysticercotic encephalitis have also been described [4]. Another group of Cestodes is the *Echinococcus* which causes hydatidiform lesions [4-8]. Some species of these parasites are prominent in the Middle East and South America, while other strains are prominent in Asia. This latter species, *Echinococcus multilocularis* is of small size and can get into the lung. Originally this species spread from the cold Artic and Alaska by fox and today can be found in domestic and migratory animals, like the rodents, cat and dog. Another species of *Echinococcus*, *Echinococcus granulosus*, resides mostly in dogs with the parasites harboring in their intestine. The vascular flow and the lymph drainage transmit the parasite to other organs in the body including the brain. A cyst or multiple cysts then form inside the CNS with the larger in forms of grape cluster which can be revealed by CT or MRI [1,9]. Since the cysts exist chronically for many years, they can generate daughter cysts and in the human, have been known to grow as large as 50 cm and contain more than one liter of fluid [2]. Multiple cysts is particularly common in the alveococcus which lives in the liver and brain [2]. Cysts caused by *E. multilocularis* are usually found within brain parenchyma, while those by *E. granulosus* can be found in brain parenchyma, the ventricular system, subarachnoid space, epidural space and spinal canal [4]. Biochemically, the patients can also be confirmed by serum Indirect Hemagglutination (IHA) or Enzyme Linked Immunosorbent Assay (ELISA) [10]. CNS involvement will produce headache due to increase of intracranial pressure. Nausea and seizures may also be produced. Since the hydatid cyst is well encapsulated, there will not be any spread from a cyst into other regions of the CNS. Like all parasitic diseases, eosinophilia is observed in the blood.

Immature forms of tapeworm can also be a source of CNS parasitic problem. This is illustrated by the *Spirometra* which is common in Asia, particularly in countries in which the population likes to eat raw fish as the parasite normally is harbored in the fish. As a consequence, populations in Japan, Korea and part of China are most susceptible. After ingestion, the parasites change their host into human, cats and dogs [11-13]. Sometimes, the eggs of these parasites are found in invertebrates like crab, shrimp or crayfish and upon ingestion of these raw, they change another host. The parasite, when rests in the mammalian host, inhabits initially inside their intestine. The interesting part is the parasites can get out of the gastrointestinal tract and produce subcutaneous nodules which are shown to be migratory. For some reason and mechanism still unknown, the nodules can migrate to the brain, causing seizure and headache. As the nodule increases in size (multiple parasites growing together), the mass is big enough to compress on neurons and tracts to produce paralysis. This is a slow growing parasite and the growth can take several decades. Like some other parasites mentioned later in this review, the *Spirometra* or its relative species can also spread to the eye, causing severe pain during growth due to blockage and increase in intraocular pressure, especially when the growth is near the limbus of the eye. Finally, the infection will lead to blindness. ELISA is the best biochemical diagnosing method; CT imaging can show calcified circular structures. A ring-shaped surrounding is possibility related to substantial vascular changes including edema [14-16].

A similar worm to the Platyhelminthes (tapeworm) is of a total different category. This is the nematodes or round worm which had been documented for more than two centuries in Africa and in Japan. These are the worms which cause the edema of lymphatic vessels in the leg resulting in elephantiasis [17]. Of course, the round worm presented in other areas like causing subcutaneous nodules and migrating into the retina and the sub conjunctiva causing Onchocerciasis or black river blindness [17]. The host could be cattle, horse and dog and human and the vector is the blackfly [17]. The adult worm in the host gives off microfilaria as larval form carried by the vector to infect another host. In the dog, microfilaria can go into the heart as well and are known as heart worms. In the human, the microfilaria can migrate from the eye into the blood vessel in the brain forming granulomas which is tuberculoid in form containing macrophages which may produce calcified profiles upon imaging *Wuchereria bancrofti* Identification of the parasite is by scanning for microfilaria in blood, immunoprecipitation essay and imaging.

The second type of parasite infesting the brain is the group of trematode or the flukes. Well known examples include *Paragonimus* sp. which are found mostly in Africa and Asia [18]. They are present in crustacean of freshwater and if eaten raw, will go into the intestine of the host including domestic animals and human. In the intestine, the larva can migrate into the thoracic cavity and seek refuge in the lung. Its migration from the lung to the brain has not been scientifically sought out and there are suggestions of venous migration or via foramina to the basal areas of the brain [19,20]. Like the *Spirometra*, subcutaneous nodules with the parasites end out initially in the abdomen and go towards the lung and upwards. Those to the brain will induce a meningoencephalitis with headache, muscular weakness, seizure and spinal involvement [21]. CSF eosinophil is diagnostic and X ray revealed soap bubble gatherings and CT shows calcification spots[1].In the brain, these parasitic species usually invade into the temporal and occipital lobes, causing lysis, hemorrhage and gliosis [2].

Other than *Paragonimus*, the fluke *Schistosoma* which is of huge importance in Asia, especially in China and Japan, is worthy of mentioning [22]. There are several species of this genus showing migration of the parasite into the brain, notably *Schistosoma japonicum* [23]. The famous liver fluke of China *Clonorchis chinensis* had not been reported to migrate to the brain [2]. Again, *Schistosoma* is a water-related fluke and has an intermediate host of the snail. The general story is that the larva of *Schistosoma* penetrates the skin of the host and migrate upwards in the venous system. It is known that the larva (miracidium) can secrete lytic enzyme to aid the penetration [2]. While in the CNS, the parasite will not further develop but wall itself off with a capsule. A granuloma is therefore visible in the brain [1,2,24]. Larger immature parasite of the genus infest in the spinal cord instead. The detrimental part of these CNS parasites is that they initiate vast immune reaction via its exudate and cause a lot of necrosis. But this reaction is a long chronic episode, causing much edema and gliosis. Literature reported that the brain pathological loci include a wide range of areas like the parietal, temporal, occipital lobes, cerebellum and pituitary gland [2]. Involvement of the pituitary will affect the hormonal system. Apart from the usual CNS sign and symptoms, because of the chronic and massive necrosis, there is to be a massive loss of function including cognition. Diagnosis is possible with CSF ELISA IGG. With CT scan perilesion edema is prominent while MRI will illustrate dichotic and continuous chains of nodules.

The third group of parasites which will go into the brain are the protozoa or unicellular parasites. Well known examples are *Trypanosoma* and amoeba.

Trypanosoma is frequently reported in the central and southern part of America and its route of spread can be 1) bite by a bug (*Triatoma* sp.) which carries stages of the parasite 2) ingested infected animals or 3) via transplants and transfusion [25]. By far 1) is the most prominent route. The larvae then go into the skin of the host and mature intracellularly inside the organs [26]. Headache, joint pain and asthenia are all reactions related to host response and often there is palpebral edema as one of the reactions Meningoencephalitis in the CNS can be detect in the CSF via microscope or ELISA. Imaging shows ring-like effect surrounding lesion.

Another *Trypanosoma* is the one that cause sleeping disease in Africa usually with the species name of *Trypanosoma brucei* and carried by the tsetse fly. After the skin lesion, the parasite migrates via the lymphatic system and the tricky parasite can continuously change its surface glycoprotein to evade the immune system of the host. Again invasion into the brain produce massive reaction. The meningoencephalitis attracts a lot of exudates, swelling, edema and in addition hemorrhage. The intracranial increase of pressure compresses usually on the hypothalamus, brainstem and the cerebellum, thus interrupting biological rhythm, autonomic activities, producing ataxia and nausea as well as pyramidal and extrapyramidal motor activities [27]. Antibody or PCR assays on the blood or CSF are diagnostic. Most of the imaging lesions are actually on the white matter more than the grey matter [1].

The other protozoa group is of course those of Amobae. *Naegleria fowleri* is notorious in stagnant freshwater ponds and infection usually started from the nose to the nasal cavity and ascends to lyse the cribriform plate and enter the basal forebrain. Then they may stay at the olfactory bulb or break through the meningeal spaces to infect the basal brain, brainstem and the posterior part of brain and cerebellum [28,29]. Death may come within days. On the other hand, patients with infection limited to only the choncha may still be alive after months but their face will be disfigured and the nose, nasal septum and the meatus and choncha might be gone. The blood picture is a leukocytosis. ELISA and PCR must be quickly performed in view of the very acute downhill episode [30].

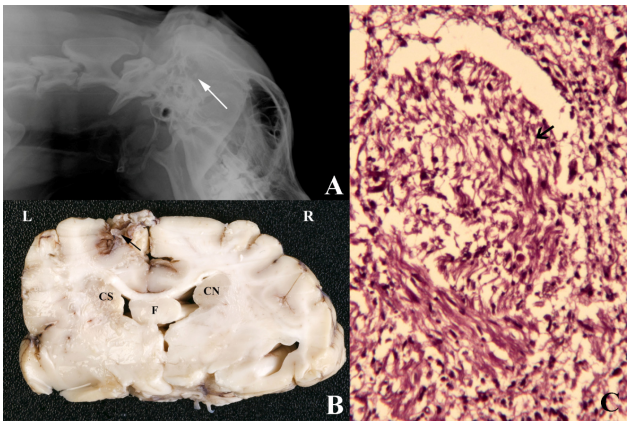
One of the most frequently encountered amoeba species is the Amoeba *(Acanthamoeba) histolytica* [31,32]. For the nervous system, the A histolytica affects mostly the cornea and appearing in freshwater, contaminated water and soil, this protozoa can get onto contact lens and resulting in corneal keratitis [33,34]. In the brain, cysts or abscess are seen, usually as meningitis. Imaging usually revealed a ring-like lesion surrounding the cyst or abscess, probably because of the large amount of edema [1].

Babesia is another protozoa which has zoonotic importance and generally overlooked. One of the genus Babesia divergens which is normally in rodents, cattle, gerbils, monkeys and can affect human and has been termed as red water fever [35]. It is generally a parasite that similar to malaria, attacks red blood cells and thus would be located in the blood vessels of the host. The vector is the tick Ixodes ricinus. Patients with immunodeficiency are most vulnerable as seen in the experiment of splenectomized monkeys as well as in human patients. Infected animals and human will demonstrate fever, anemia, anorexia and hemoglobiuria. Usually the protozoa can be maintained for years in human erythrocyte and can be inoculated into the host [35]. There are two stages of the parasite, a ring stage with clear cytoplasm and a lontrophozoite stage with pointed heads on both poles and in fact we have observed both stages in the brain of the host. With the large amount of the protozoa filling the blood, the parasites can migrate through blood vessels (capillaries) to the brain. With the uprising of cases involved with pets which showed migration of Babesia into the brain, we have now beginning to take Babesia seriously as an important pathological agent not only for the general vascular malady, but for the disease in the nervous system which usually leads to fatal consequences. In fact, a case we experienced with suggested that Babesia may enter the nervous system directly instead of via a vascular mean.

In fact, babesiosis and toxoplasmosis are two prominent protozoa infections which involved the nervous system and the eye in the dog, and the vivid example of the latter is the *Toxoplasma gondii* which infects both dogs and cats. It is estimated to have infected one-third of the world's population [36]. The clinical episodes include fever, seizures, tremors, muscle weakness, vomiting, abdominal pain, and loss of appetite. The eyes, because of their close association of the brain, were usually involved as well, perhaps through spread of the CSF or via vascular and lymphatic channels. Presence of gondii as well as white blood cells were seen in the CSF while low white cell quantities (leucocytes and lymphocytes) was observed in the peripheral blood. This parasite in fact completes its life cycle in the infected dog or cat and passed out the pathogen via the faeces. As a form of cyst, along with a mucous abundant diarrhea. Menigitis and cephalomyelitis were CNS components of the complex disease and are responsible for the tremor, seizure and muscular weakness [37]. Vomiting may be a reaction of the gastrointestinal system but can also be the reaction of autonomic activation due to lesion of the brain. These overall CNS symptoms were very familiar to the CNS episode of babesiosis. In both cases, the infection of the eye was in common as well. The ocular lesion includes retinitis, uveitis and keratitis and the investing parasite will produce cell death and scarring of the retina, iris and the cornea [37]. Iris inflammation will disturb the iris angle and the filtering system of the trabecular meshwork, hence inducing glaucoma. Glaucoma, with retinal cell death and corneal cell lesion will all lead to scarring and loss of vision at the end stages of ocular parasitic lesion by these two parasites. The inflammatory changes on all important parts of the eye will predispose much edema, resulting in a very painful eye which is also an illustrative feature of these two forms of infection. Slit lamp infection may at times be able to see the parasites itself in the anterior chamber of the eye, sometimes mistaken as floaters.

The recent experiences we had with babesiosis were all from household pets, in particular golden retriever dogs. The signs and symptoms include anorexia, convulsion, unilateral circling behavior, difficult initiation of motor activities as well as tremor. Upon necropsy, the brains and spinal cords looked normal grossly, with the exception that there were small areas of degeneration usually

on the temporal or basal part of parietal look, usually ipsilateral. Routine X rays indicated dense lesions deep to the cortex which is not encapsulated (Figure 1A). Coronal sections revealed cotton wool like degenerative lesions in the corpus striatum, mainly in the caudate nucleus (Figure 1B). Microscopic inspection of the areas revealed degeneration of fibers and pyknosis of neurons (Figure 1C). High power (630X) magnification indicated pathology of endothelial cells of blood vessels (Figure 2) and invasion of protozoa into both red cells and neurons (Figure 3). In the neurons, the protozoa exhibit two stages intracellularly. One is a ring-like circular form inside the neuron. It appears this was the immature form while the other was a long protozoa penetrating the cell. Lymphocytes and macrophages formed giant cells were present in the scene (Figure 3).



Figures 1(A-C): Figure 1A: Possible lesion spot in the cortex of a dog via X-ray. Figure 1B: A coronal section of the middle of the brain. Swelling of fronices can be seen (F), as well as difference in sizes of the caudate nucleus (shrinked caudate (CS) vs. normal caudate (CN)). L: left side; R: right side. (x1.3). Note many white spots on the pathological caudate. Possible atrophy of the cortex. Figure 1C: Whorls of degenerating nerve fibers (arrow) in the affected caudate. (x100).

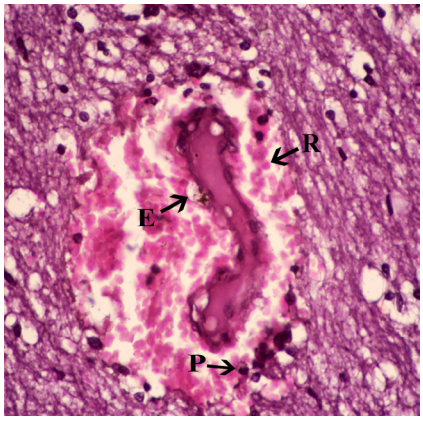


Figure 2: Large blood vessels of affected area displayed swollen endothelial cells (E), red cell (R) (some pathological in appearance) surrounding vessels and parasite inside groups of red cells (P). (x630).

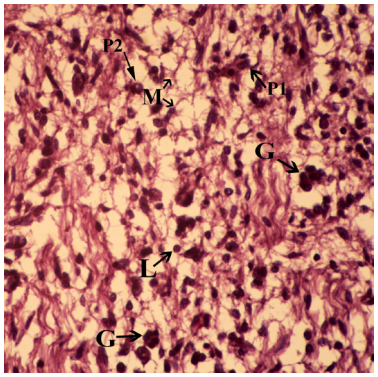


Figure 3: The affected area with possible parasite (P) in macrophage. Giant cells (G), lymphocytes (L) and microglia (M) were seen. (x630). P1: Adult protozoa P2: Immature protozoa vesicular stage – ring-shaped. Both in host cells.

One of the most virulent forms of encephalopathy is the mad cow disease or its corresponding Creutzfeldt Jacob encephalopathy in the human. This is a prion disease containing tubulofilamentous particles of prion protein [38]. The disease was first discovered in the cows in the United Kingdom in 1986. Histologically appearance is the presence of large vacuoles inside the cytoplasm of neurons and hence the term spongioform encephalopathy. In the parasitic encephalopathy of our type, large vacuolations inside the neurons are rare although there are some small spaces. Diagnosis relies on the presence of parasite inside the neurons and the serological antibody tests. In this type of encephalopathy, clinical symptoms of encehalopathy of course lead to muscular weakness and dystonia. As in spongioform encephalopathy, walking is with much difficulty in animals. Because the lesion is more discrete at times, seizures are frequent. One interesting additional point is that in several of the dogs with the disease observed, the lesions in the corpus striatum are particularly evident. As such, it appears that the subcortical lesions are always around this area. As a consequence, the infected dogs show a circular rotation and tend to lean on a solid partition, e.g. a wall to avoid further turning. The involvement of the lentiform nucleus displays neurons with parasitic fragments, along with white cells (leucocytes and lymphocytes nearby). The presence of the latter may be related to secondary bacterial infection or antibody production. Of most obvious prevalence is the formation of giant cells inside the histological picture and since giant cells usually originated from macrophages, the invasion has attracted macrophages. Indeed, one is able to spot the macrophages in the pathological slides of the brain. From the point of degeneration, one can see nerve fibers in edema and in fragmentation, thus suggesting that the parasite will somehow induce fiber degeneration. Parasites inside myelin sheaths of nerve fibers had not been noted suggesting that nerve fiber degeneration is not physical, unlike the penetration of neurons by parasites. The lesion of the lentiform nucleus is appealing in that no lesion in the

surrounding thalamus is observed. If one considers that the parasite may invade via the branches of the deep perforating vessels of the vascular system, the lenticulostriate artery or the choridal arteries, then one would wonder why the thalamus would not be affected. The counter argument of this is of course the number of the parasite inside the brain matters. Perhaps the number is not vast in quantity. The investment of the parasites in the corpus striatum (to be specific the lentiform nucleus) of course produce extrapyramidal syndromes and in addition the proximity of motor fibers in the internal capsule would likely be compressed leading to pyramidal syndromes as well. It is imperative to remember that with the increase of zoonotic diseases in the world, due to more interactions between wild, domestic animals and pets, the rise of parasitic diseases may also be on the verge of rising and species changing hosts and carriers may emerge to new heights. Understanding these diseases before it gets to human at a large scale is of significantly urgency.

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