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## Neurologic Manifestations of *Leishmania* spp. Infection

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Received 1 April 2011; Revised 7 April 2011; Accepted 9 April 2011

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**Abstract** When listing common clinical signs of the spectra of *Leishmania*-derived diseases, neurologic malfunctions are not commonly included. Despite this, there are multiple reported instances both in human and veterinary medicine where neurologic manifestations, whether central or peripheral, are described. In this review, we describe neurologic manifestations seen during infection with *Leishmania* spp. with some discussion of the implicit effect of inflammation on the blood brain barrier in both medical and veterinary cases. Taken together, the material discussed here suggests that in patients from *Leishmania*-endemic areas, when observing neurologic symptoms, causation secondary to infection with *Leishmania* spp. should be highly considered.

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### 1 Introduction

Leishmaniasis is a parasitic vector-borne disease caused by a family of obligate intracellular dimorphic protozoa of the genus *Leishmania* (Figure 1). Although there is a spectra of clinical forms seen with different species of *Leishmania* parasite, this infection is not classically associated with neurologic manifestations. Despite this, there is a wealth of clinical information on neurological effects of leishmaniasis in animal models [14, 15, 37] and human case studies [21], which indicates that both central nervous system (CNS) and ocular manifestations are common and often under-reported. There are historical [5] and recent reports [1] of both CNS and ocular alterations with visceral leishmaniasis (VL), particularly. In addition to CNS manifestations, there have been studies indicating localized peripheral nerve deficits with cutaneous leishmaniasis [25]. On the whole, neurologic manifestations may occur with *Leishmania* infection much more frequently than discussed in overview descriptions of this complex infectious disease process.

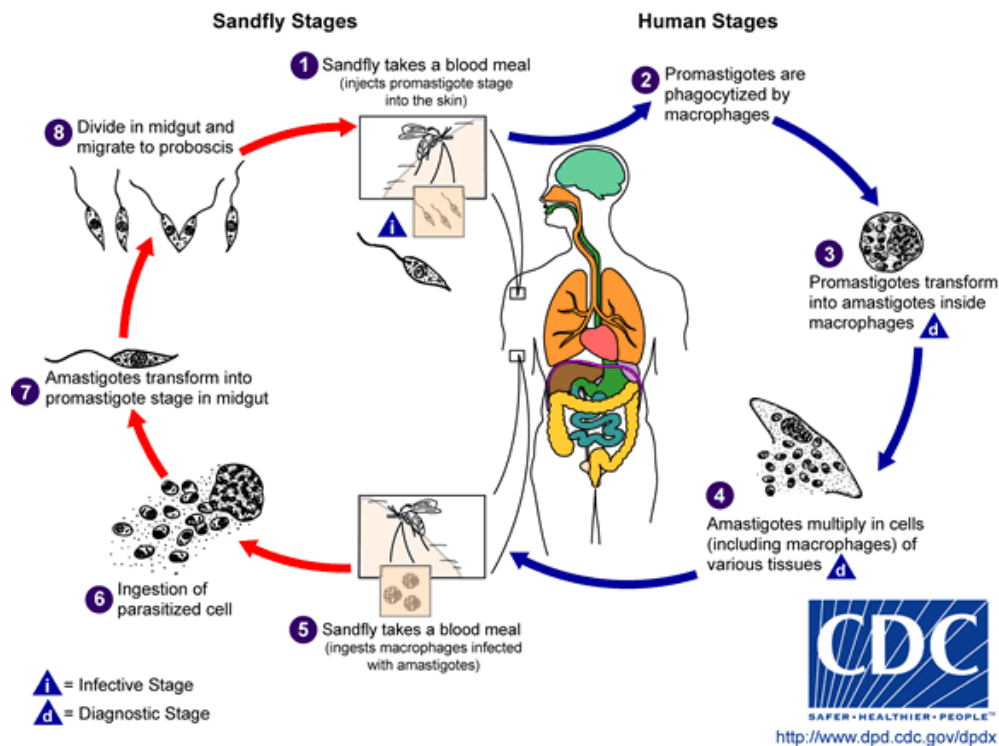
### 2 Historical case reports of neurologic manifestations during *Leishmania* infection

Visceral leishmaniasis (VL), also known in humans as Kala-azar, meaning “black sickness” for the increased pigmentation observed on the skin of the face, feet and hands in patients in the Bihar region of India, has been recognized as a disease for centuries. At the turn of the twentieth century, British pathologists studying “dum-dum fever” patients in India reported finding amastigotes in brain meninges [44]. On gross examination of VL patients from East Africa, it is common to find widely disseminated parasites, including in the cerebrospinal fluid and in the endothelia of meningeal vessels [44]. In Northern Africa, paralytic symptoms were reported to be associated with VL, which would resolve after treatment with pentavalent antimony [44]. A report from the mid-1960s described neurologic disturbances in patients infected with VL [36]. Mental changes are also commonly reported; Carswell indicated that “although patients can walk 20 miles to the dispensary, they had a most curious mental depression and were completely apathetic” [5]. “Definite metal changes” in 3 of 18 patients were described in a collection of clinical cases from Ethiopia [29].

Regarding cutaneous leishmaniasis (CL), a report investigating associated distal nerve involvement in cutaneous lesion biopsy specimens in the 14 affected biopsies described an overall perineural inflammatory cell infiltrate consisting of either lymphocytes or a mixture of lymphocytes, plasma cells, and macrophages [25]. In this report, four patients had inflammatory cell invasion of the nerves (neuritis), and in one of them the inflammation was granulomatous and associated with nerve destruction. Amastigotes were seen inside the perineural sheath in two patients. Sensory testing of 50 consecutive patients with cutaneous leishmaniasis identified two patients with diminished sensations in the area of their CL lesions [25]. A study of hyperesthetic CL patients with follow-up mechanistic

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**Figure 1:** *Leishmania* life cycle. Credit to CDC.

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studies using *L. major* infection in BALB/c mice nerve sheath inflammation and parasites within the perineural space occurred with some frequency, though nerve inflammation did not correlate with persistence of the cutaneous lesion [46].

### 3 Recent case reports of neurologic manifestations during *Leishmania* infection

More recent case reports from the last two decades also indicated that neurologic abnormalities in *Leishmania*-infected patients are not unusual. A report from Sudan which followed 111 patients described neurologic signs in 46% of the patients in this study, the most common of which was the sensation of burning feet and foot drop with less frequent to rare deafness and cranial nerve deficits [21]. In most patients these neurological signs diminished or went away altogether after initiation of anti-*Leishmania* therapy. A separate report of VL in 10-year-old boy who was not responsive to initial therapy indicated that this patient also had parasite-related meningitis. When this patient was treated with an anti-leishmaniocidal regimen of Amphotericin B, his meningitis resolved [43]. Finally, there are reports of patients who have cutaneous and ocular manifestations of leishmaniasis after renal transplant and immunosuppression [20].

### 4 Evidence in animal models of neurologic manifestations during *Leishmania* infection

VL transmission is primarily vector borne via the sand fly, with dogs and humans as natural host species [45]. Infected dogs are the primary reservoir for zoonotic visceral leishmaniasis in endemic regions, and are the most significant risk factor predisposing humans to infection [17]. The range of vector-borne canine VL is expanding, leading to new areas where human infection occurs [34]. Chemotherapy of canines is often unsuccessful, providing continued transmission risk from infected dogs to humans. Canine clinical signs often mirror symptoms which are reported in human patients, and neurologic manifestations are no exception.

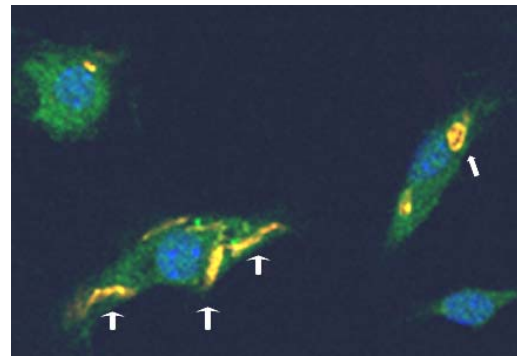
Although the most common CNS finding is infiltration of inflammatory cells during VL infection of dogs [33], there are reports of presence of amastigotes in both choroid plexus [37] and meninges [49] (which was confirmed via immunohistochemistry in experimental infection [48]). It is also reported to be not uncommon to see ocular changes with canine VL [30]. Similar to the reports of vagueness or apathy in human patients [5,36], in a report of Leishmaniasis in U.S. hunting dogs the dog's caretaker noted neurological signs including "altered states of mind", seizures, hind limb paralysis and loss of scenting ability [2]. A diffuse non-suppurative meningoencephalitis

with scattered areas of necrosis in grey matter and diffuse vacuolation in the white matter with gliosis in both white and grey matters was found in these *Leishmania*-infected dogs. Previous studies of Foxhounds in early 2000's found that dogs chronically infected with VL sometimes presented with a chief complaint of atypical behavior, particularly transient aggression, photophobia, hyperesthesia, paralytic episodes and seizures [24]. All dogs were current on their rabies vaccination and were not positive for rabies upon post-mortem analysis. We more recently have noted that loss of balance, particularly in the front end, and disorientation (Petersen, unpublished findings) are not uncommon in foxhound dogs which we observe as part of our ongoing studies [18,41,42]. Beyond these more typical locations of parasites and neurologic malfunction, there is a report of infection of tongue leading to cranial nerve deficits [13].

Rodents are also found to be naturally infected with particularly cutaneous forms of leishmaniasis, although a version of visceralizing disease can be found in BALB/c mice and golden Syrian hamsters. Studies dating back to the 1920's demonstrated neurologic manifestations of infection with VL in hamsters [31]. Similarly, BALB/c mice have been shown to have CNS-tropic VL [16].

## 5 Disruption of the blood brain barrier

Reports of neuro-inflammation associated with natural and experimental VL infection [1,33], as well as the presence of Immunoglobulin in aqueous humor and cerebrospinal fluid (CSF) [15] suggest a disruption of the blood-brain barrier (BBB), and the blood-cerebrospinal fluid barrier underlies the CNS manifestation of disease. The BBB functions to exclude microscopic objects and large hydrophilic molecules, and is achieved by endothelial cell specializations including tight junctions between cells, a specialized basal lamina surrounding the vessels in the brain, and an ensheathment of the vessels made of astrocytic endfeet [11]. Under normal physiological conditions, the BBB would prevent the entry of intracellular amastigotes and subsequent inflammatory cells observed with VL (Figure 2). The BBB can be disrupted by matrix metalloproteinases (MMPs), which are major extracellular matrix degrading enzymes [4]. There have been reports of MMP 2 and 9 expressions in animals with VL [27,28,32] though it is unclear if (1) this is the mechanism that underlies BBB disruption and infiltration of leukocytes and (2) what is the underlying cause of MMP expression.



**Figure 2:** *Leishmania amazonensis* amastigote (narrow head arrow) and promastigotes (broad head arrows) within murine dendritic cells, labeled with a parasite specific antibody (yellow), nuclei labeled with DAPI (blue), 100× magnification, fluorescence microscopy. Through infection of monocyte-lineage cells, parasites make their way into the CNS.

## 6 Ocular manifestations subsequent to neurologic manifestations during *Leishmania* infection secondary to inflammation

Given the pervasive nature of *Leishmania* infection and its ability to cause inflammation in the central nervous system, it is not therefore surprising that ocular manifestations are also somewhat common. Most frequently the clinical presentation of ocular leishmaniasis in humans is anterior uveitis either prior to or just after presumed successful treatment of visceral leishmaniasis. Less frequently parasites are found in the orbit [9,10]. Uveitis can progress to secondary glaucoma [9], a disease of retinal cells. Retinal hemorrhages have been observed on fundic examination; in some cases multiple lesions were reported (> 10 lesions in each eye) [8,35]. In a more severe case, these lesions appeared to be 'flame-shaped' potentially arising from hemorrhages from arteriolar capillaries of the nerve fiber layer. In all reported cases, there was a correlation with at least moderate-to-severe anemia with thrombocytopenia. These retinal hemorrhages resolved after treatment for leishmaniasis and improvement of the secondary anemia/thrombocytopenia. In one unusual case, mucosal leishmaniasis presented as optic neuropathy and sinusitis [23].

Similarly, regarding canine visceral leishmaniasis, it is not uncommon to perceive uveitis during chronic systemic canine VL [14,15]. There were measurable levels of anti-*Leishmania* IgG within the aqueous humor and cerebrospinal fluid as measured by ELISA; these levels did not correlate with serum antibody levels. There was a marked inflammation of multiple ocular structures including

the ciliary processes, ciliary body, iris and lacrimal duct and presence of amastigote parasites [14, 15].

### 7 Ocular abnormalities secondary to facial mucocutaneous disease

Within the literature, there are multiple cases of involvement of eyelid during clinical cutaneous or mucocutaneous leishmaniasis [38], with a granulomatous infiltrate in four out of five cases and observable parasites within the touch preparation in two patients. All five patients in this series [38] had positive leishmanin skin tests and eyelid lesions which resolved with anti-*Leishmania* therapy. Although rare, severe manifestations of eyelid involvement have been described which altered vision. As an example, a lesion which led to bilateral ptosis and lower eyelid ectropion secondary to cutaneous leishmaniasis caused a severe exposure keratopathy [6]. Although not a primary ocular lesion, a chronic dacryocystitis with mucocutaneous leishmaniasis has been described in multiple patients, which led to ocular abnormalities due to problems in tear film formation [3].

### 8 Endo-ocular parasitism

The first case to report *Leishmania sp.* isolated from aqueous humor in a (human) patient with disseminated CL and bilateral non-granulomatous iridocyclitis [12] was in Brazil. The ophthalmologic lesions were unresponsive to therapy despite resolution of the other systemic and cutaneous manifestations of this disease, which led to a fine needle aspirate of the anterior eye and isolation of *Leishmania sp.* This rare finding is in contrast to canine disease where 25% of canine VL cases have ocular manifestations [39], with a range of 16–80% in various case studies [7, 19, 30, 40, 47]. In the most recent review, a granulomatous inflammatory infiltrate was found and in 32 of 120 eyes (26.6%) with a parasite that is identified immunohistochemically within the globe [39]. Ocular tissues found to be affected, in order of frequency, were conjunctiva and limbus, ciliary body, iris, cornea, sclera and iridocorneal angle, choroid and the optic nerve sheath. Different histopathological patterns were identified in each of these ocular structures. *Leishmania* organisms and associated inflammation were found in different ocular tissues, accounting for ocular clinical signs described with canine VL [39]. There have been three cases of feline ocular leishmaniasis reported [22, 26]. In the most recent case, initial ophthalmic examination revealed bilateral deep stromal corneal ulcers, exudative panuveitis and secondary glaucoma. Although a specific topical treatment was applied, melting ulcers progressed to corneal perforation and both eyes were enucleated. Ocular histopathology showed large numbers of intracellular

organisms compatible with amastigotes of the genus *Leishmania* in the uvea, cornea, sclera and retina. Results of immunohistochemical staining on ocular samples were positive for *Leishmania* [26].

### 9 Conclusions

Although not frequently thought of as “classical” clinical signs or symptoms of clinical leishmaniasis, neurologic manifestations of particularly visceralizing leishmaniasis is not uncommon in either human or other mammalian infection. When determining the cause of visual deficits in either human or canine patients that come from endemic areas for leishmaniasis, a fundic exam may be diagnostic and provide further insight on the overall case. Both central and peripheral nervous system alterations have been shown to occur with leishmaniasis.

**Acknowledgment** This work was supported by National Institutes of Health grant AI50803.

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