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Cerebral Toxocariasis: Silent Progression to Neurodegenerative Disorders?

Chia-Kwung Fan,[a,b]* Celia V. Holland,[c] Karen Loxton,[c] Ursula Barghouth[d]

Department of Molecular Parasitology and Tropical Diseases, School of Medicine, Taipei Medical University, Taipei, Taiwan[a]; Master Program in Global Health and Development, College of Public Health and Nutrition, Taipei Medical University, Taipei, Taiwan[b]; Department of Zoology, School of Natural Sciences, Trinity College, Dublin, Ireland[c]; A. T. Still University School of Osteopathic Medicine in Arizona, Mesa, Arizona, USA[d]

SUMMARY

Toxocara canis and *T. cati* are highly prevalent nematode infections of the intestines of dogs and cats. In paratenic hosts, larvae do not mature in the intestine but instead migrate through the somatic tissues and organs of the body. The presence of these migrating larvae can contribute to pathology. *Toxocara* larvae can invade the brains of humans, and while case descriptions of cerebral toxocariasis are historically rare, improved diagnosis and greater awareness have contributed to increased detection. Despite this, cerebral or neurological toxocariasis (NT) remains a poorly understood phenomenon. Furthermore, our understanding of cognitive deficits due to toxocariasis in human populations remains particularly deficient. Recent data describe an enhanced expression of biomarkers associated with brain injury, such as GFAP, AβPP, transforming growth factor β1 (TGF-β1), NF-L, S100B, tTG, and p-tau, in mice receiving even low doses of *Toxocara* ova. Finally, this review outlines a hypothesis to explore the relationship between the presence of *T. canis* larvae in the brain and the progression of Alzheimer's disease (AD) due to enhanced AD-associated neurodegenerative biomarker expression.

INTRODUCTION

Helminths of the genus *Toxocara* belong to the class Nematoda, order Ascaroidea, and superfamily Ascaridoidea. Among a total of 21 species within the *Toxocara* genus, 2 are of significant public health concern, namely, *Toxocara canis* and *T. cati*, for which dogs and cats, respectively, are the definitive hosts. After ingestion of food or water contaminated by infective *Toxocara* eggs, larvae hatch in the small intestine, penetrate the gut wall, and are transported to the liver and lungs via the blood circulation. Subsequently, the larvae undergo a further migration by the tra-

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Address correspondence to Chia-Kwung Fan, tedfan@tmu.edu.tw.

* Present address: Chia-Kwung Fan, Department of Molecular Parasitology and Tropical Diseases, School of Medicine, Taipei Medical University, Taipei, Taiwan.

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cheal route to mature to adulthood in the small intestine. In general, patent infections occur in dogs 4 to 5 weeks after infection (1, 2) and in cats 8 weeks after infection (3). Dogs and cats may acquire patent infections throughout their lives through accidental ingestion of eggs or via consumption of encapsulated larvae within paratenic hosts. In addition, puppies, unlike kittens, may be infected by the transplacental route (4).

Surveys of *T. canis* in dogs demonstrate wide ranges of infection prevalences globally, with 86 to 100% prevalence in puppies and 1 to 45% prevalence in adults (5–9). Reports of the prevalence of *T. cati* infection include 38.3% of Spanish stray cats (10), 79% of stray cats in Denmark, and 91% of feral cats on farms in the United Kingdom (11). A recent study from Japan (12) indicated that in samples from 34 sandpits taken in the Tokyo metropolitan area, 41.2% (14/34 samples) were contaminated with *T. cati* eggs as examined by PCR analysis. *T. cati* may play a more important role in human toxocariasis than previously recognized; for example, a number of studies suggest that *T. cati* is the causative agent of ocular toxocariasis (OT) (11, 13).

Nonembryonated *T. canis* eggs are shed with the feces, and embryonation occurs in the soil over a period of 2 to 5 weeks, in a process which is influenced by both temperature and humidity (14). Infectivity of eggs occurs within 54 days at 12 to 18°C, whereas the time to attain infectivity is shortened to 14 days at 25 to 30°C. *Toxocara* eggs are extremely resistant to physical and chemical agents, and in temperate climates, they are able to survive well over winter, for 6 to 12 months. Survivability of eggs under moist, cool conditions may be as long as 2 to 4 years or more (15). However, several factors affect the development and survival of eggs, as well as the availability of eggs to potential hosts, including temperature, light, humidity, pH, the substrate and vegetation cover, and physical dispersal of eggs by definitive hosts or through the actions of birds, rainfall, flies, beetles, earthworms, and slugs. In addition, the potential role of drinking water and the recreational use of water in transmission cannot be ignored (16). Of particular note, Fan et al. (17) utilized *T. canis* embryonated eggs which had been preserved in 2% formalin for at least 14 months at 4°C to inoculate ICR outbred mice. Larvae recovered from the liver and brain at 469 days postinfection were still alive. Furthermore, these larvae were capable of causing various degrees of Th2-related granulomatous inflammatory injuries to internal organs, such as the liver and lungs, indicating that pathogenicity and infectivity were retained even after long-term storage in 2% formalin.

IMMUNODIAGNOSTICS IN INVESTIGATIVE CLINICAL PRACTICE

The fact that *Toxocara* larvae do not develop to maturity but remain as larvae within paratenic hosts, such as humans, has implications and challenges for diagnosis (18, 19). In such paratenic hosts, *T. canis* L3 larvae neither molt, grow, nor replicate and will wander through a number of internal organs in humans so as to cause neurotoxocariasis (NT), ocular toxocariasis (OT), or visceral larva migrans (VLM) (19, 20). Therefore, diagnosis in the context of investigative and clinical practice predominantly depends upon immunological techniques. These include an enzyme-linked immunosorbent assay based on *T. canis* larval excretory-secretory (TESELISA) antigens or the use of fractionated TES antigens for Western blotting (TESWB), although recombinant antigens used for both serological methods have also been produced and proven to be more specific than TES (21). Although the sensitivity and specificity of TESELISA are reported to be 91% and 86%, respectively, antigenic cross-reactivity greatly reduces accuracy, particularly in subtropical and tropical regions, where polyparasitism is common (19). In contrast, increased specificity can be obtained with TESWB due to reactivity to bands at 24 to 32 kDa that are specific to *T. canis* infection (19). The detection of IgG subclasses has been found to be more effective for immunodiagnosis of *Toxocara* sp. infection. In particular, IgG2 antibodies specific to the glycan of *Toxocara* excretory-secretory antigens yields the highest sensitivity, though at a reduced specificity (22), while the use of IgG4 as the secondary antibody significantly increases specificity (23). Since IgG4 may reflect prolonged antigenic stimulation (24), this antibody subclass could be useful for monitoring larval viability before and after treatment (25).

T. canis larvae can remain viable for prolonged periods in paratenic hosts, maintaining elevated levels of immunoglobulins (26); therefore, determining whether an infection is acute or chronic has remained a significant challenge to date. In toxocariasis, the avidity of specific IgG cannot be determined using specific IgM levels, as IgM antibodies are detected throughout infection (25).

Alternatives to traditional ELISA, such as methods of measuring antibody avidity, have been proposed (26, 27). Methods that measure antibody-binding properties in chronic infections, and their optimization, have been described (28). The avidity of antibodies increases from low to high during the course of infection. Based on this, a method to selectively unbind antibodies by utilizing chaotropic agents, which can disrupt the hydrogen bonding network between macromolecules, i.e., proteins, nucleic acids, and water molecules, by weakening the hydrophobic effect (29), is used to determine the age of a range of infectious diseases (30). This method has been shown to be useful for the diagnosis of toxoplasmosis seroconversion in women during pregnancy (31). Therefore, it seems promising for making a diagnosis of recent *Toxocara* infections by assessing the IgG avidity. One study has supported the view that high IgG avidity occurs in chronic infections and low IgG avidity in the early phase of infection (26). Furthermore, clinical observations among 11 Polish children suffering from acute toxocariasis described an initially low IgG avidity. Follow-up over a 6- to 12-month period revealed that specific IgG avidity levels increased significantly in all children except one (32). Nevertheless, further studies concerning whether IgG avidity is applicable as a diagnostic index of recent *T. canis* infection are required for validation of this method. Diagnosis can be reached definitively through biopsy of affected tissue, but biopsy specimens are rarely available. In contrast, in cases where toxocariasis is suspected, PCR detection of *Toxocara* sp. DNA sampled from affected tissues is applicable (33).

SEROPREVALENCE AND ASSOCIATED RISK FACTORS IN GENERAL POPULATIONS

A Brief Review of Global Seroprevalence

Worldwide seroepidemiological surveys as assessed by IgG antibody level reveal that human toxocariasis is among the most frequently occurring helminthiases. In Western countries, such as the G8 nations (United States, Japan, Canada, Germany, United Kingdom, Italy, France, and Russia), seroprevalence is highest in rural areas, ranging from 35% to 42%, and it falls to 15% to 20% in

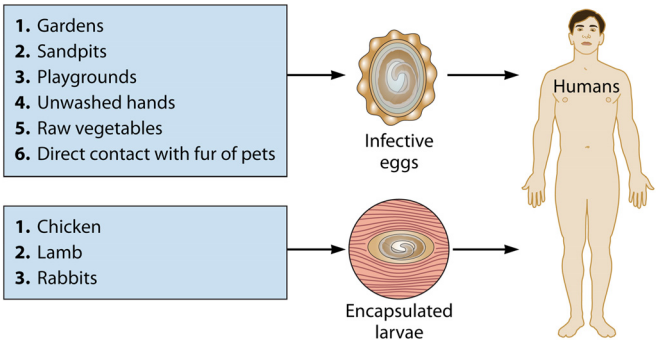

FIG 1 Potential routes of transmission for *Toxocara canis* infection to humans via the oral route. Infection through consumption of chicken, lamb, or rabbit is rare.

semirural zones and 2% to 5% in urban areas (25, 34). For example, even in the United States, *Toxocara* sp. infection is reportedly one of the important childhood zoonotic infections and is more prevalent in African American communities and individuals living in poverty (35). In contrast, higher seroprevalences are reported from developing countries, for example, Nigeria (30%), Brazil (36%), Swaziland (44.6%), Malaysia (58%) Indonesia (63.2%), Nepal (81%), Marshall Islands (86.8%), and La Reunion (93%) (36–39). However, an accurate analysis of seroprevalences between different countries and studies is hindered by the different methodologies used to detect infections (WB or ELISA), different cutoff titers, and the difficulties in linking infection, titers, and symptomatic disease (19, 40). Importantly, seroepidemiological data indicate that exposure to *T. canis* infection is widespread and, as a potential cause of significant disease, should not be ignored.

Risk Factors

Humans may acquire *T. canis* infection by several routes, such as accidental ingestion of soil contaminated with eggs (playgrounds, sandpits, and gardens), from unwashed raw vegetables and hands, or from the hair of pet dogs and cats (Fig. 1) (20, 41). Infections caused by ingesting encapsulated larvae in raw or undercooked infected organs or muscle tissues from paratenic hosts, such as chicken, lamb, or rabbit, have been reported from adults in northeastern Asian countries, e.g., Japan or South Korea, albeit rarely (Fig. 1) (20, 42–49). However, successful infection is influenced by a number of exposure- and susceptibility-related factors, including cultural and socioeconomic factors, environmental, geographic, and host immunity, genetics, age, gender, nutrition, coinfection, and the behavior of human and definitive hosts (20, 50, 51). Additionally, international migration and urbanization, with urban areas now containing upward of 50% of the world's population, result in increased interactions between humans and definitive hosts, which contributes to *Toxocara*/toxocariasis being an ever-changing public health concern (50).

Companion animals may provide benefits with regard to socialization and physical and mental well-being (52), but potential health hazards of *T. canis* infection related to pet ownership should be not overlooked (52). A variety of studies from different geographical locations have shown that embryonated *T. canis* eggs can be recovered from the coats of dogs, suggesting that exposure to dogs may increase the risk of infection to humans (41, 53–56). However, Keegan and Holland (57) demonstrated that owned dogs that had been cared for properly had very few eggs on their hair and that none of these were embryonated, suggesting that direct contact with such dogs is not a high risk factor for infection. Recently, a study from the United States, a country with more than 93 million cats and 77 million dogs (58), showed that both geographic and individual-level risk factors, e.g., pet ownership, are associated with *Toxocara* sp. seroprevalence (59). Additionally, problems with untreated and uncontrolled definitive hosts result in environments that are heavily contaminated with *T. canis* ova, which, along with geophagia, poor hygiene, lower education levels, and poverty, provide ideal transmission opportunities, particularly in warmer climates. Host genetics ultimately determines susceptibility or resistance to parasite infection through innate or acquired immunity (60). Therefore, the role of genetic factors and immunological parameters in predisposition to infection with helminths was recently emphasized (61), and the relevance of these observations to *Toxocara* sp. infection should be explored further.

TYPES OF HUMAN TOXOCARIASIS AND IMMUNOPATHOGENESIS

In human toxocariasis, migrating L3 *T. canis* larvae are responsible for the clinical syndromes observed. Larvae move through the bloodstream to various organs, including the liver, heart, lungs, kidneys, brain, muscle, and eyes. Symptomatic disease manifestations depend on the infection intensity, the duration of migration, the organs involved, and immune- and age-mediated host responses (20). Currently, both pediatric and adult patients with toxocariasis report a wide variety of inflammation-related conditions, such as asthma, pneumonia, lymphadenopathy, endomyocarditis, granulomatous hepatitis, generalized endophthalmitis, meningoencephalitis, and cutaneous manifestations (33, 62–69). Notably, the focus of much research has been on the role of *T. canis* in neuropathological disorders, particularly epilepsy (70–73). Quattrocchi et al. (72) demonstrated a highly significant association between people with epilepsy (PWE) and antibodies to *Toxocara* (see details in "Seizure," below). However, Magnaval et al. concluded that cerebral invasion by *T. canis* larvae rarely induces a recognizable neurological syndrome in humans, but instead that infection is correlated with the association of a number of risk factors, including contact with dogs, which may result in repeated infections with small numbers of larvae (74). However, it was noted that a German woman with cerebral toxocariasis also presented with depressive symptoms and cognitive deficits (75). Exploration of the relationship occurring between host and parasite in the brain may elucidate the cryptic symptoms of human toxocariasis, with patients presenting with mental disability, epilepsy, and other central nervous system (CNS) disorders (18).

Due to the range of clinical manifestations of toxocariasis observed over the last 30 years, two main forms of human toxocariasis were established in 1988: VLM and OT (76). A third form, common or covert toxocariasis (CT), was described in 1992 and 1993 for patients who were seropositive and presented with weakness, gastrointestinal disorders, and lethargy (77, 78). Human toxocariasis is currently classified clinically into four types, including VLM, OT, CT, and NT (19, 20, 66). Regarding toxocariasis immunopathogenesis, TES antigens have been found to play a pivotal role in triggering granulomatous inflammation, a mani-

festation of delayed-type hypersensitivity mediated by Th1 cells, as well as IgE, eosinophilia, and enhanced cytokine expression (e.g., interleukin-13 [IL-13], IL-5, and IL-4) characteristic of Th2-mediated responses (79).

Immunological defenses of the host are influenced by a number of environmental and genetic factors and the interaction between them. Evidence suggests that infection with *Toxocara* is associated with a polarized $CD4^+$ Th2 response with elevated IgE levels and eosinophilia, mediated by human leukocyte antigen (HLA) class II molecules. HLA class II molecules have been linked to disease severity and host genes affecting exposure-related behaviors (60). A role for $Foxp3^+$ $CD4^+$ $CD25^+$ T regulatory (Treg) cells in the regulation of immunopathology, including granuloma development in murine models of toxocaral hepatitis, and in the enhanced expression of transforming growth factor β1 (TGF-β1) was recently suggested. TGF-β1 is important for the function and local survival of Treg cells during larval migration in the muscle, small intestine, brain, and liver of the mouse (80–82). The potential susceptibility loci of HLA class II molecules are considered to be involved in regulating Th2-dominant immunity (controlled by $Foxp3^+$ $CD4^+$ $CD25^+$ Treg cells by stimulation through TGF-β1), creating an environment that benefits larvae but potentially contributes to organ damage (81). However, the immunological and molecular mechanisms associated with TGF-β1/Th2 responses resulting in protection against or resistance to *Toxocara* sp. invasion, along with associated pathological changes, need further investigation. Nevertheless, the TGF-β1 Leu10Pro variant has been highlighted as being significantly associated with microfilaria loads in human lymphatic filariasis disease (83), but whether this has a role in toxocariasis disease severity is not known.

Because the Th2-dominated granulomatous inflammatory response and the associated raised antibody titers and eosinophilia do not control or eliminate *Toxocara* sp. larvae, *T. canis* larvae *per se* may be capable of evading host immunological attacks (84). *T. canis* larvae contain a mucin-rich, highly labile surface coat which is shed when antibodies and/or eosinophils bind, allowing the parasite to escape from attack by the host's immunity (84). Although eosinophilia can frequently be seen in clinical toxocariasis, evidence is lacking for a protective role for eosinophils in toxocariasis, as larvae remain unharmed in mice overexpressing IL-5, to induce a resultant hypereosinophilia. In contrast, the intestinal nematode of mice *Nippostrongylus brasiliensis* is eliminated (85). Furthermore, when *N. brasiliensis* is introduced into transgenic IL-5 mice in the presence of TES antigens, the mouse survival rate is greatly enhanced (86). It appears that TES antigens are important in the orchestration of immune evasion/manipulation, which is likely to be a mechanism by which *T. canis* facilitates its long-term survival in the host (84). In addition, TES antigens are capable of killing T lymphocytes (Th2 cells) by triggering caspase-dependent apoptosis, as evidenced by enhanced caspase-9 expression in TES antigen-cocultured T lymphocytes *in vitro* (C.-K. Fan, unpublished data).

Visceral Larva Migrans

In 1952, Beaver and colleagues (87) used the term "visceral larva migrans" to describe a group of symptoms associated with eosinophilic granulomas containing *Toxocara* sp. larvae in the livers of children with anemia, respiratory symptoms, geophagia, enlarged liver, and extreme hypereosinophilia. Later experimental work in mice demonstrated that a high burden of larval infection or repeated infection may result in VLM (79). Although classical VLM typically occurs in young children, the frequency of VLM in adults is relatively high in northeastern Asian countries, e.g., South Korea and Japan, including those patients who became infected by eating raw beef, lamb, chicken, or ostrich liver (47–49).

Infected children may present with a persistent cough which can be treated with anthelminthics (88). However, most pathology associated with VLM occurs in the liver. In Brazil, a study of 24 autopsy cases of granulomatous lesions in the livers of children from the Children's Reference Hospital found that eosinophil-rich granulomas in 10 children (41.7%) stained positive with polyclonal anti-*Toxocara* serum (89). The pathological findings demonstrated that the hepatic granulomas possessed epithelioid cells and multinucleate giant cells forming a palisade around amorphous eosinophilic material or necrotic debris. Mononuclear cells and eosinophils were frequently observed in granuloma outer layers, and the study showed that the most frequent cause of granulomatous hepatitis in Brazilian children was VLM granulomas (89). In addition, in Poland, Hartleb and Januszewski (90) reported one female patient with chronic liver disease presenting as multiple small mass lesions and fibrous perihepatitis that was immunologically diagnosed to be caused by *T. canis* infection. Occasionally in toxocaral hepatitis, computed tomography detects low-density lesions as multiple nodules in the liver (67). The other potential clinical findings and symptoms include fatigue, headache, fever, vomiting, diarrhea, asthma, anorexia, weight loss, and abdominal pain (47).

While it is not obvious why symptomatic VLM develops, the involvement of the host immune response to larval antigens is of central importance. The immune response to the larval antigens includes elevated eosinophilia and hypergammaglobulinemia (eosinophils and IgG and IgE antibodies as manifestations of Th2-type cells) and cytokine production, e.g., secretion of IL-4, IL-5, and IL-13 by Th2-type cells. TES antigens are highly likely to prompt the induction of this population of Th2-type cells. The continued production of larval antigens stimulates the immune response, with the accompanying production of IgE antibodies and eosinophils. The main function of eosinophils is antibody-dependent elimination of large parasites through cell-mediated cytotoxicity (91). IL-5 regulates the accumulation of eosinophils in inflammatory tissues and modulates eosinophil maturation, recruitment, and survival. IL-4 induces B-cell class-switch recombination to IgG4 and IgE and upregulates production of major histocompatibility complex (MHC) class II molecules, while reducing production of gamma interferon (IFN-γ), IL-12, Th1 cells, and macrophages, as well as dendritic cell production of IL-12 (92). Tissue macrophages are important in wound repair and chronic inflammation. IL-4 in extravascular tissues induces the alternative, M2 form of macrophage activation and inhibits classical activation of macrophages into M1 cells, which differentiate in response to cytokines and express many characteristics of tissue macrophages (93). An increase in M2 macrophages, along with the simultaneous secretion of IL-10 and TGF-β, reduces damaging inflammation, resulting in further development of wound healing and/or fibrosis (94).

Ocular Toxocariasis

Wilder (95) first described ocular larva migrans (OLM) after detecting lesions containing larvae in the eyes of children with suspected retinoblastoma. OLM, which is currently named OT, is

TABLE 1 Differential diagnosis between ocular toxocariasis and retinoblastoma[a]

Parameter	Description	
	Ocular toxocariasis	Retinoblastoma
Morphology	Centrally located mass with moderate enhancement revealed by MRI	Nodular in contour and lies along the posterior pole of the globe
Enhancement	Moderate uveoscleral enhancement or enhancement of a granuloma	Usually characterized by moderate or avid enhancement
Calcification	Rare	Punctate or speckled calcification in more than 90% of cases
Demographics	Patients usually 5–10 years of age	Observed before 5 years of age in more than 90% of cases, average age at diagnosis is ~18 months
Signs and complications	Usually presents with unilateral visual loss, and pain and redness are common presenting symptoms	Leukocoria in more than half of cases; strabismus is the second most common presentation, occurring in ~20% of cases

[a] Based on data from reference 110.

thought to be rare compared to VLM and results from infection with small numbers of *T. canis* larvae. OT has the highest incidence in young children from the age of 5 to 10 years (96), with damage to vision which is unilateral and accompanied by intermittent strabismus caused by *T. canis* L3 migration in the eye and resultant immune reactions (20). Accidental ingestion of small numbers of *T. canis* ova as a result of being consistently exposed to environments that are contaminated with ova may lead to OT, reflecting why *Toxocara* sp. antibody titers are usually lower in OT cases than VLM cases (96).

Fan et al. (20) reviewed case reports of toxocariasis from PubMed for the period between 1990 and 2012, which included 290 papers and 368 OT cases. The largest number of cases was in Europe (97), followed by Asia (98), North America (62), Latin America (27), Australia (5), and Tunisia (1). Japan, France, Brazil, and the United States had the largest numbers of reported cases in Asia, Europe, Latin America, and North America, respectively.

Although the manifestations of OT range from asymptomatic to severe (99), most reported cases have been accompanied by symptomatology. According to a review paper by Arevalo et al. (96), three major clinical types of OT syndrome have been suggested, based on the severity of manifestations, including diffuse nematode endophthalmitis, the peripheral inflammatory mass type, and the posterior pole granuloma type (100–102). In general, patients with OT have a normal white blood count, normal serum IgE level, and no eosinophilia (96). Substantial clinical evidence indicates that the most common presentation of OT is a granuloma found in the peripheral retina, seen in 50% to 64% of cases, with a posterior pole granuloma seen in 25% to 36% of cases and endophthalmitis seen in <25% of cases (102, 103). Over 50% of cases are unilateral ocular infections presenting with mild ocular inflammation, but if the infection is persistent, bilateral disease may be manifested (104). Stewart et al. (103) analyzed 22 patients from San Francisco with OT between 1977 and 1996, and they reported cases of acute inflammation (36.4%), chronic inflammation (31.8%), and recurrent inflammation (31.8%). Damage to vision occurs over days or weeks, with the location of the larvae, the extent of eosinophilia, and the possible development of a fibrotic granulomatous response determining the level of impairment. The presence of granulomas can result in blindness due to heterotopia and/or detachment of the macula and distortion (98, 105).

Visual impairment can be found in most cases of OT, that is, with a visual acuity of less than 20/40 at presentation (normal vision is commonly referred to as 20/20 vision), with a median between 20/200 and 20/400 in eyes with endophthalmitis, a median of 20/70 in eyes with peripheral granuloma, and a median of 20/50 in eyes with a posterior pole granuloma (103). Larvae are most commonly located in the peripheral retina and vitreous, with larvae occurring in one or both of these sites. An ill-defined, hazy white lesion may be observed in the periphery or posterior pole, with various degrees of vitreous inflammation. After resolution of the inflammatory reaction, the lesion appears as a well-defined elevated mass in the periphery, along with folding in the inner retinal layer which may extend toward the macula. Endophthalmitis does not produce much pain and causes minimal external damage, but it can be accompanied by marked vitritis, a secondary cataract, and a mild anterior chamber reaction (99). Macular detachment may result from uveitis that causes vitreomacular traction or epiretinal membrane and puckering of the macula. Traction may lead to retinal breaks in the atrophic retina, creating a combined tractional rhegmatogenous detachment. An optic papillitis can also occur, usually because of an invasion of the nerve by *T. canis* larvae or if there is inflammation due to the parasite being situated elsewhere in the eye (106). Gass et al. (107) first described diffuse unilateral subacute neuroretinitis (DUSN) due to *Toxocara* spp., and another possible presentation of OT, i.e., bilateral DSN, has also been suggested (107, 108). However, in prolonged *Toxocara* sp. infection, chorioretinitis may be followed by choroidal neovascular membrane formation (14). A recent study from Pennsylvania indicated that 22 of 604 patients within whom pseudoretinoblastomas were identified were found to have OT, indicating that ophthalmologists should avoid misdiagnosing OT as a retinoblastoma (109). A differential diagnosis between OT and retinoblastoma based on morphology, enhancement, calcification, demographics, signs, and complications has been suggested by Small and Schaefer (110) (Table 1). In fact, the diagnosis of OT remains challenging and, in the majority of cases, is only presumptive. Standard diagnostic methods for OT are fundoscopy, imaging, and serologic testing (102). Although the sensitivity and specificity of TESELISA for immunodiagnosis of VLM are fair, the sensitivity for diagnosis of OT syndrome is considerably lower (96). However, the detection of antibodies at any level will support a *Toxocara* uveitis diagnosis if the possibility complies with the clinical presentation (103, 111). Since establishment of the diagnosis of OT based solely on clinical features and serologic results is considered unreliable, some ophthalmologists recommend the addition of *Toxocara* sp. Goldman-Witmer coefficient (GW) determination [GW = (level of specific IgG in aqueous humor/level of specific IgG in serum)/(total IgG in aqueous humor/total IgG in

serum)] to aid in patient diagnosis of idiopathic focal chorioretinitis or vitritis. A cutoff value of ≥3 for GW is considered to confirm intraocular antibody synthesis related to active *Toxocara* invasion (96, 104). Imaging studies, particularly ultrasound examination and computed tomography, are also useful (112).

Coinfections with *T. canis* and other parasites, such as *Toxoplasma gondii*, may exacerbate impaired vision. As *Toxocara* spp. and *T. gondii* share a mode of exposure, i.e., soil ingestion, it was suggested that infections with these parasites may be correlated. A study utilized serum samples obtained during the U.S. Third National Health and Nutrition Examination Survey (NHANES III; 1988–1994), from children aged 12 years and younger, to determine the prevalence of antibodies to *Toxocara* spp. and *T. gondii* and to examine coinfection risk factors. After adjusting for risk and demographic factors by multivariate analysis, the results demonstrated that infection with *Toxocara* spp. was associated with almost twice the risk of infection with *T. gondii* (odds ratio [OR] = 1.93; 95% confidence limit [CL] = 1.61 to 2.31), and vice versa (OR = 1.91; 95% CL = 1.59 to 2.28) (113).

Risk factors for patients with OT include geophagy, consumption of snails and raw meat, convulsions, and prior ownership of dogs (114). Hayashi et al. (115) observed that the migratory route of *T. canis* larvae to the eye may be from the brain through the optic nerve, as assessed in one experimental study using a gerbil animal model (although the gerbil is not a natural paratenic host of *T. canis*). Other researchers postulated that it is more likely that larvae travel in blood vessels rather than by burrowing and that the route by which larvae reach the eye remains to be determined (103).

Treatment options for OT include the anthelmintic drugs albendazole and mebendazole. While data regarding the optimal duration of treatment are lacking, a 5-day course is generally sufficient. In cases where inflammation is present, corticosteroids should be prescribed. This is especially important to prevent scarring in OT patients, which may lead to permanent vision loss; therefore, patients should be monitored closely by an ophthalmologist, and surgery may be required. For example, Woodhall et al. (98) showed that cataracts are the second most common indication for surgical treatment (3 patients were treated with cataract surgery) in patients with ocular toxocariasis.

Covert or Common Toxocariasis

The observation of a high seroprevalence of *Toxocara* in many countries worldwide but a relatively small number of suspected VLM cases has led to the suggestion that clinical disease entities associated with toxocariasis, other than VLM and OT, are likely to exist (76). Evidence from two cross-sectional community studies, conducted in Ireland and France, resulted in a new clinical type of toxocariasis being described for seropositive adults and children who were asymptomatic or had mild or nonspecific symptoms. This became termed "common or covert toxocariasis" (76, 116, 117). In France, symptoms of toxocariasis in adults included breathing difficulties, rash, pruritus, weakness, and abdominal pain. Those patients showed elevated titers of anti-*Toxocara* antibodies, eosinophilia, and elevated total IgE levels. The syndrome was termed "common toxocariasis" in adults (117). The subjects were 37 adults living in the Midi-Pyrenees region of France and were age and sex matched with 37 hospital patients who served as controls. In Ireland, symptoms in children infected with *Toxocara* included pyrexia, loss of appetite, headache, nausea, emesis, lethargy, behavior and sleep disorders, abdominal pain, inflammation of the pharynx, pneumonia, cough, wheeze, itching, rash, limb pains, cervical lymphadenitis, pruritus, rash, and hepatomegaly. Normal blood eosinophil counts were found in 27% of patients exhibiting high anti-*Toxocara* titers. The syndrome in children was termed "covert toxocariasis" (76). The subjects were patients attending the National Children's Hospital, many of whom had asthma. To date, it remains a challenge to develop convincing diagnostic tests for CT, because most infections go undiagnosed due to less severe systemic manifestations and nonspecific laboratory abnormalities.

Neurotoxocariasis

The sites of CNS invasion by *Toxocara* larvae include the brain and spinal cord. Neurotoxocariasis (NT) is a CNS manifestation of *Toxocara* infection that is influenced by multiple factors, such as host genetic factors, the number of ingested ova, and previous exposure, all of which contribute to the complex pathogenesis of NT (20, 118). CNS toxocariasis in humans was first described by Beautyman and Woolf (119) in an autopsy study of a child who died of poliomyelitis, in whom a larva was found in the left thalamus. Beaver et al. (87) proposed the term VLM to account for the disease in children with long-term multisystem disease and eosinophilia. Thereafter, Nichols et al. (120) first identified and gave a full description of the egg, larva, and adult worm morphology of *Toxocara* spp., the causative agents of toxocariasis.

Magnaval et al. (74) conducted a case-control study and found that *T. canis* larval invasion of the brain rarely induces recognizable neurological signs, which may be explained by repeated low-dose infections. However, due to improved diagnosis, an increasing number of clinical NT cases due to larval invasion of the brain or spinal cord have been recorded over the last 30 years. Associated neurological damage and consequent epilepsy, neuropsychologic deficits, eosinophilic meningoencephalitis, myelitis, and cerebral vasculitis have been described (18, 33, 121). While our understanding of the mechanisms underlying human NT is incomplete, seroepidemiological surveys demonstrate high levels of exposure to *Toxocara* in the population, suggesting that NT may be an underestimated public health implication of infection (36). Recently, *Toxocara* was described as "America's most common neglected infection of poverty and a helminthiasis of global importance" (115, 122); however, the number of cases of NT will tend to be underestimated due to nonspecific clinical signs compared with VLM, as well as due to a lack of availability of appropriate testing, thus leading to possible underdiagnosis (18, 122).

Nevertheless, examination of cerebrospinal fluid (CSF) samples is worthwhile in the exploration of suspected CNS toxocariasis with abnormal neurological symptoms, since many NT cases show negative antibody levels in blood but positivity in CSF (123). The rule appears to be lower serum antibody titers than CSF antibody titers, particularly in the more common toxocaral myelopathy form of the disease (124–126). It should be noted that an antibody reaction in the serum is an unreliable indicator for evaluating disease activity in the CNS, as reactivity persists after clinical recovery (63). Some studies have outlined diagnostic criteria for NT that include high titers of antibodies to *T. canis* in the serum (evaluated by TESELISA or TESWB), eosinophilia in CSF or blood, intrathecal production of antibodies to *T. canis*, and a history of exposure to dogs (123).

However, the possibility of baylisascaris as a differential diag-

nosis for cerebral toxocariasis must not be overlooked. The nematode *Baylisascaris procyonis* infects the raccoon (*Procyon lotor*) and may rarely cause neural larva migrans (NLM), which can be devastating neurologically, or even fatal, in young children (127). *B. procyonis* larvae, unlike those of *Toxocara*, continue to grow within inappropriate hosts, e.g., humans (127). Patients with *B. procyonis* NLM often present with an eosinophilic meningoencephalitis that is severe and acute, with severe seizures that are frequent and difficult to control. Visual impairment and blindness often occur, with the majority of patients requiring complete nursing care. Diagnosis of CT versus *B. procyonis* NLM may include at least two diagnostic criteria. The first criterion is the the larger size of *B. procyonis* larvae (average length in the 2nd stage, 300 μm) and their capacity for continued growth and development during migration through the host, with *B. procyonis* larvae reaching lengths of 1,500 to 1,900 μm and diameters of 60 to 80 μm in the 3rd stage. In contrast, *T. canis* larvae reach lengths of 350 to 445 μm and a diameter of 20 μm, and notably, larvae in paratenic hosts undergo no growth (127). Second, antibodies generated against *B. procyonis* infection appear to selectively recognize periodate-resistant (protein) epitopes of larval ES antigens with molecular masses of 33 kDa to 45 kDa, which are not recognized by *T. canis* antibody-positive or normal sera (128). Additionally, several studies have confirmed that sera and CSF of children infected with *B. procyonis* test positive for antibodies to *Baylisascaris* while consistently being negative for anti-*Toxocara* antibodies (129–131).

Clinical drug trials for CNS toxocariasis treatment are lacking (126). Albendazole's lower toxicity than that of other anthelmintics and its good penetration of nervous tissues make it the medication of choice (123). Nevertheless, anthelmintic therapy may have side effects due to inflammatory reactions and edema resulting from Herxheimer's reaction (a rapid response to endotoxins released by the death of *T. canis* larvae within the body), and corticosteroids may be required from the beginning of the treatment. There have not been any studies that have proven that combined treatment with albendazole and corticosteroids is superior to single therapy (125). Corticoids may be considered in the case of immune vasculitis, though this condition is quite rare and difficult to identify (132).

GLOBAL CASES OF HUMAN CEREBRAL TOXOCARIASIS WITH VARIOUS NEUROLOGICAL DISORDERS FROM 1985 TO 2014

Since the accuracy of various diagnostic approaches for the detection of NT cases has improved greatly over the last 30 years, we undertook a search using some keywords, e.g., "*T. canis*," "toxocariasis," "brain," and "CNS," to determine the number of NT cases recorded in PubMed from 1985 to June 2014, and we found that 86 patients with various neurological manifestations have been recorded (Table 2).

Cerebral injury was recorded for a total of 24 clinical cases (28%), including 6 cases of eosinophilic meningoencephalitis, 5 cases of seizure, 4 cases of cerebral vasculitis, 3 cases of eosinophilic meningitis, 2 cases of cognitive impairment, and 1 case each of eosinophilic encephalitis, fibrotic arachnoidea, bilateral subdural hemorrhage with subarachnoid hemorrhage, and cerebral meningoradiculitis (Table 2). With respect to manifestations of spinal cord involvement, a total of 62 clinical cases (72%) have been reported, including 35 cases of myelitis, 20 cases of Viliuisk encephalomyelitis (VE) (see details in "Myelitis," below), 5 cases of (meningo)encephalomyelitis, and 1 case each of lower motor neuron disease and spinal abscess (Table 2). Note that some cases of myelopathy, urinary retention, and bowel dysfunction were reported, because *T. canis* larvae may cause compressive and noncompressive pressure to the spinal cord, resulting in myelopathy (133–135). Further analysis of the clinical NT cases listed in Table 2 demonstrated that Europe and Asia had the same number of cases (44 cases), followed by the Americas, with 8 cases. Only one case was reported from Africa (South Africa) (Fig. 2). Distribution by country revealed that Sakha Republic, Lebanon, and France reported the largest numbers of NT cases (20, 17, and 7 cases, respectively) (Fig. 2). The number of cases with cerebral involvement revealed that Europe had the largest number (16 cases), followed by 5 cases in the Americas and 2 cases in Asia (Fig. 2). In contrast, cases with myelonic involvement were highest in Asia (42 cases), Europe (28 cases), and the Americas (3 cases), with only 1 case reported from Africa (Fig. 2). These patients with NT, with either cerebral or myelonic involvement, were predominantly adults. The average age for 86 patients with NT was 41.3 ± 16.7 years, and males (41.6 ± 14.6 years) and females (41.0 ± 18.7 years) had similar ages. The average age of patients with cerebral involvement was 34.7 ± 23.6 years, and female patients (37.5 ± 25.7 years) were older than male patients (30.7 ± 21.1 years); in patients with myelonic involvement, the average age was 43.7 ± 12.8 years, and male patients (44.7 ± 9.4 years) were older than female patients (42.6 ± 14.8 years).

As shown in Table 2, 41% (35/86 cases) and 24% (21/86 cases) of NT cases had eosinophilia detected in blood and CSF, respectively, emphasizing the importance of eosinophilia as a diagnostic criterion for NT (121). Moreover, most NT cases can be detected by medical imaging techniques. Imaging techniques such as computed tomography and magnetic resonance imaging (MRI) are very useful tools for detecting and localizing lesions caused by migrating *Toxocara* sp. larvae in neural tissues, thus supporting a tentative diagnosis of NT (134–137). In fact, the more sensitive MRI method can reveal granulomas as hyperintensities on T2-weighted MRI sequences, located mainly cortically or subcortically in brain areas (134, 137, 138).

To conclude, although there are clearly increasing numbers of reports of cerebral or myelonic injury cases caused by *T. canis*, it remains perplexing that the exact prevalence of CNS involvement in toxocariasis is currently unknown, and information on the impact of NT on human neuropsychology remains sorely lacking (18, 121).

Eosinophilic Meningoencephalitis, Meningitis, and Encephalitis

Of the NT cases listed in Table 2, there are 5 cases of eosinophilic meningoencephalitis, 3 cases of eosinophilic meningitis, and 1 case of eosinophilic encephalitis, and all of them presented with eosinophilia in the blood or CSF. Clinical cerebral toxocariasis disease is associated with the severity of inflammation and damage caused to the CNS and with the number of larvae invading the brain (139). The symptoms of eosinophilic meningitis were described by Vidal et al. (63) for a 2-year-old boy who presented with mental confusion, fever, headache, tachycardia, hyperreflexia, dyspnoea, lethargy, irritability, motor weakness, and nuchal rigidity. Initial lumbar puncture revealed 23% eosinophils in the CSF (the level is <1% under healthy conditions), and thereafter, an eosinophilic pleocytosis persisted in the CSF. Both IgG antibodies

TABLE 2 Neurological manifestations in neurotoxocariasis cases from 1985 to June 2014[a]

CNS involvement	Neurological manifestation; patient description	Diagnostic tests and findings	Medication	Country	Reference
Brain	Cerebral vasculitis; 66-year-old woman	11% eosinophils in CSF; anti-*T. canis* IgG antibody in the blood and CSF (ELISA, WB)	Improved spontaneously without any anthelmintic treatment	France	230
	Cerebral vasculitis; 75-year-old woman	50% eosinophils in blood; MRI; anti-*T. canis* IgG antibody in the blood and CSF (ELISA, WB)	Albendazole plus dexamethasone	Austria	231
	Cerebral vasculitis; 45-year-old man	Anti-*T. canis* IgE antibody in the blood and CSF (ELISA); cerebral angiography	Unknown	France	144
	Cerebral vasculitis; 49-year-old man	Anti-*T. canis* IgE antibody in the blood and CSF (ELISA)	Anthelmintic treatment	France	144
	Eosinophilic meningitis; 11-year-old girl	30% eosinophils in CSF; anti-*T. canis* IgG antibody in the blood (ELISA)	Diethylcarbamazine	Britain	232
	Eosinophilic meningitis; 17-year-old boy	75% eosinophils in CSF; MRI; anti-*T. canis* IgG antibody in the blood and CSF (ELISA)	Albendazole	South Korea	49
	Eosinophilic meningitis; 54-year-old man	Computed tomography; anti-*T. canis* IgG antibody in blood (WB) and *Toxocara* DNA in CSF	Albendazole plus corticosteroids	Italy	33
	Eosinophilic encephalitis; 48-year-old woman	57% eosinophils in blood; MRI; computed tomography; indirect immunofluorescence test; IQ of 90 reduced to 55 (WIP)	Diethylcarbamazine plus fenbendazole plus prednisone	Germany	132
	Eosinophilic meningoencephalitis; 18-year-old man	Eosinophilia in blood; computed tomography; anti-*T. canis* IgG antibody in the blood (ELISA)	Thiabendazole plus dexamethasone	Brazil	233
	Eosinophilic meningoencephalitis; 2-year-old boy	58% eosinophils in CSF; MRI; anti-*T. canis* IgG antibody in the blood and CSF (ELISA)	Albendazole plus dexamethasone	Brazil	63
	Eosinophilic meningoencephalitis; 54-year-old woman	36% eosinophils in CSF; computed tomography; MRI; anti-*T. canis* IgG antibody in the blood and CSF (ELISA)	Albendazole plus methylprednisolone	Greece	118
	Eosinophilic meningoencephalitis; 5-year-old girl	57% eosinophils in CSF; MRI; anti-*T. canis* IgG antibody in the blood and CSF (ELISA)	Albendazole	Brazil	234
	Eosinophilic meningoencephalitis; 45-year-old man	70% eosinophils in blood; computed tomography	Albendazole plus prednisolone	France	235
	Eosinophilic meningoencephalitis; 54-year-old woman	10% eosinophils in CSF; anti-*T. canis* IgG antibody in the blood and CSF (ELISA)	Albendazole plus methylprednisolone	USA	236
	Bilateral subdural hematoma and a small subarachnoid hemorrhage; 2.5-year-old infant autopsy	NA	NA	Britain	143
	Fibrotic arachnoidea; 53-year-old woman	Granulomatous mass with *Toxocara* larva identified by histopathology	Surgery	Italy	237
	Cerebral meningoradiculitis	Eosinophilia in the CSF; anti-*T. canis* IgG antibody in the blood and CSF (immunodiagnostic)	Unclear	France	238
	Seizure; 1-year-old boy	58% eosinophils in blood; computed tomography; anti-*T. canis* IgG antibody in the blood (ELISA)	Thiabendazole plus prednisolone	USA	182
	Seizure; 26-year-old woman	6% eosinophils in blood; computed tomography; cranial MRI; anti-*T. canis* IgG antibody in the blood (ELISA)	Diethylcarbamazine	Germany	137
	Epileptic seizure; 7-year-old girl	9% eosinophils in blood; computed tomography scan and MRI; *T. canis* larva identified in histological section	Mebendazole	Poland	239
	Seizures; 13-year-old girl	Computed tomography scan, MRI, histopathology	Albendazole	India	181
	Epileptic seizure; 11-year-old girl	9.5% eosinophils in blood; computed tomography scan, MRI; anti-*T. canis* IgG antibody in the blood (ELISA)	Albendazole	Switzerland	70
	Cognitive impairments and dementia; 65-year-old woman	Eosinophilia in CSF; computed tomography; EEG; anti-*T. canis* IgG antibody in the CSF (ELISA)	Albendazole	Germany	75
	Cognitive impairments; 45-year-old man	Normal eosinophils in CSF; MRI; anti-*T. canis* IgG antibody in the blood and CSF (WB)	Albendazole plus prednisolone	Germany	2
Spinal cord	Myelitis; 43-year-old woman	8% eosinophils in blood; *T. canis* larva detected in CSF	Thiabendazole	China	124
	Myelitis; young woman	Eosinophilia in blood and CSF; anti-*T. canis* IgG antibody in the blood and CSF (ELISA)	Diethylcarbamazine	France	147
	Myelitis; 23-year-old woman	11% eosinophils in CSF; anti-*T. canis* IgG antibody in the blood and CSF (ELISA)	Thiabendazole plus mebendazole plus dexamethasone	USA	145
	Myelitis; 58-year-old man	50% eosinophils in blood; MRI; anti-*T. canis* IgG antibody in the blood (ELISA)	Mebendazole plus methylprednisolone	Belgium	240
	Myelitis; 54-year-old woman	40% eosinophils in CSF; spinal MRI; anti-*T. canis* IgG antibody in the blood and CSF (ELISA)	Mebendazole plus methylprednisolone	Belgium	125
	Transverse myelitis; 5-year-old boy	57% eosinophils in CSF; anti-*T. canis* IgG antibody in the blood and CSF (ELISA)	Thiabendazole for 15 days	Brazil	234
	Transverse myelitis; 5-year-old girl	15% eosinophils in blood, 57% eosinophils in CSF; MRI; anti-*T. canis* IgG antibody in the blood and CSF (ELISA)	Thiabendazole for 14 days plus albendazole for 10 days	Brazil	234

Myelitis; 32-year-old woman	50% eosinophils in CSF; MRI; anti-*T. canis* IgG antibody in the blood and CSF (ELISA)	Mebendazole	France	241
Myelitis; 37-year-old woman	11% eosinophils in CSF; brain MRI; anti-*T. canis* IgG antibody in the blood and CSF (ELISA)	Albendazole	Japan	134
Myelitis; 40-year-old woman	10% eosinophils in CSF; MRI; anti-*T. canis* IgG antibody in the blood and CSF (ELISA, WB)	Albendazole plus prednisolone	Japan	134
Myelitis; 8 men (mean age, 48.5 yr)	MRI; anti-*T. canis* IgG antibody in the blood (ELISA)	Albendazole plus steroid/no improvement	South Korea	114
Myelitis; 14 men (42.8 ± 11.0 yr) and 3 women (31.0 ± 9.9 yr)	47.1% of patients with eosinophilia in blood; MRI	Albendazole plus steroids	Lebanon	138
Lower motor neuron disease; 51-year-old man	Normal eosinophil counts in blood and CSF; anti-*T. canis* IgG antibody in the blood and CSF (ELISA, WB)	Albendazole plus diethylcarbazine (LMND remained in progress)	Austria	242
Eosinophilic meningoencephalomyelitis; 21-year-old woman	30% eosinophils in CSF; anti-*T. canis* IgG antibody in the blood and CSF (ELISA, WB)	Diethylcarbamazine plus prednisolone	Japan	148
Meningomyelitis; 49-year-old man	37% eosinophils in CSF; MRI; anti-*T. canis* IgG antibody in the blood and CSF (ELISA)	Albendazole plus steroids	Germany	146
Eosinophilic meningomyelitis; 39-year-old man	>40% eosinophils in CSF; MRI	Albendazole plus prednisolone	Germany	123
Encephalomyelitis; 2-year-old girl	11% eosinophils in CSF; MRI; anti-*T. canis* IgG antibody in the blood and CSF (ELISA)	Thiabendazole plus prednisolone	Brazil	243
Intracranial and intraspinal abscesses; 38-year-old man	26% eosinophils in blood; MRI; computed tomography scan; *Toxocara* larva was identified	Lost to follow-up	India	244
Encephalomyelitis; 45-year-old man	21% eosinophils in blood and 9% eosinophils in CSF; MRI; anti-*T. canis* IgG antibody in the blood and CSF (ELISA)	Albendazole plus methylprednisolone	Belgium	135
Chronic Viliuisk encephalomyelitis; 3 males and 17 females (51.9 ± 14.0 yr)	13 patients had eosinophilia in blood; MRI; anti-*T. canis* IgG antibody in the blood and CSF (WB)	No treatment records described	Sakha Republic	151

[a] NA, not available; WIP, a shortened form of the Wechsler intelligence test; LMND, lower motor neuron disease.

in CSF and serum were reactive to *T. canis*. MRI of the brain identified a single hyperintense lesion, and an electroencephalogram (EEG) showed severe diffuse cerebral involvement. Treatment in the form of albendazole combined with corticosteroids was given, and the general condition of the boy at a 3-month follow-up was improved, though he showed some motor weakness and poor muscle tone in the lower limbs, as well as moderate paralysis and uncontrolled spasms in the right arm.

Xinou et al. (118) described a woman aged 54 years presenting with gait disturbance, clumsiness in the left arm, behavioral disorders, and an eosinophilia of 36%. EEG showed a diffusely, mildly slowed background and focal slow activity in and from the left hemisphere. T2-weighted MRI showed multiple hyperintense lesions in the occipital and right frontal lobes, which computed tomography examination showed as hypodense areas in the white matter. The serum was positive for IgG antibodies against *T. canis*, but the CSF was negative. The patient's condition improved rapidly after an initial treatment scheme combining albendazole and methylprednisolone, except for some residual clumsiness and weakness of the left arm.

Cerebral *T. canis* infections may rarely manifest as eosinophilic encephalitis. Sommer et al. (132) reported a 48-year-old patient with *T. canis* encephalitis presenting with ataxia, rigor, and disturbances of memory and concentration. Imaging revealed both localized and diffuse white matter lesions and middle cerebral artery branch occlusion. Anthelmintic therapy was effective initially, but due to progression of CNS symptoms, immunosuppressive therapy and corticosteroids were given.

In addition to serological or molecular diagnostic methods, medical imaging techniques, such as computed tomography and MRI, are important for the detection and localization of lesions caused by migrating *Toxocara* sp. larvae in neural tissues (134–138). MRI images of the brain may show clearly defined, multifocal lesions with strong contrast enhancement or, for persistent infections, both diffuse and circumscribed changes, but these are nonspecific findings. Several reports provided descriptions of imaging of cerebral toxocariasis cases, including numerous cortical, subcortical, or white matter lesions that were hyperintense on T2-weighted MRI images, hypoattenuating on computed tomography scans, and homogeneously enhancing. It was noted that the center of one occipital lobe lesion was hyperattenuating on computed tomography scans and hyperintense on both T1- and T2-weighted MRI images, which was suggestive of microhemorrhages or cortical necrosis due to cerebral infarction. Granulomas on the initial MRI also showed strong homogeneous enhancement, possibly due to a localized disruption of the blood-brain barrier (BBB) as a result of inflammation (118, 135, 138).

There is no general agreement on the usefulness of corticosteroids for the treatment of CNS toxocariasis. Prednisolone was shown to have a beneficial effect on eosinophilic meningitis due to the nematode *Angiostrongylus cantonensis*, suggesting a role for corticosteroids in the treatment of *T. canis* eosinophilic meningitis (140). In addition, Jung et al. (141) demonstrated that the efficacy of albendazole could be increased approximately 50% by simultaneous administration of dexamethasone. Some studies have indicated that patients with intense inflammatory responses causing serious neurologic symptoms benefit from corticosteroid therapy (142), although some case reports of toxocariasis symptoms, e.g., granulomatous lesions or meningitis (without encephalitis), have described spontaneous remission with anthelmintic treatment

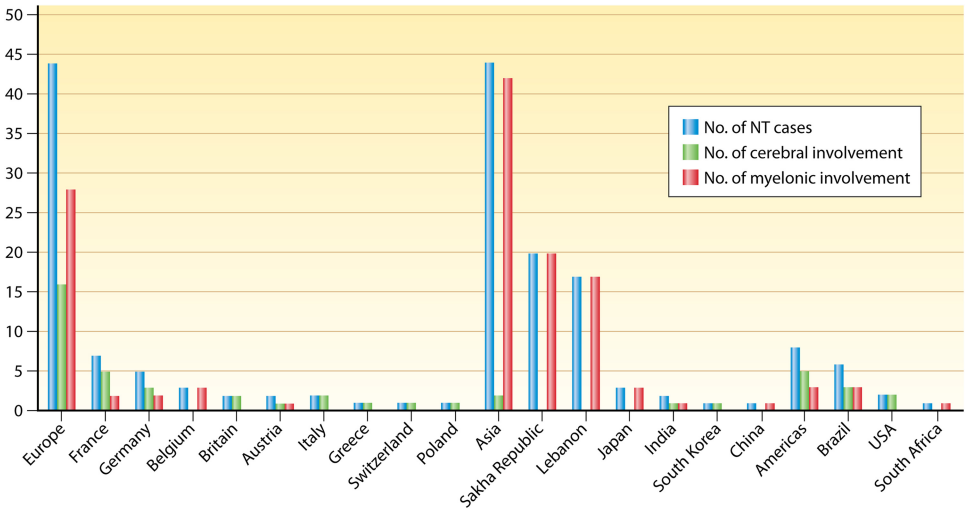

FIG 2 Numbers of neurotoxocariasis (NT) cases—totals and those with cerebral and myelonic involvement—analyzed among 86 clinical NT cases in the PubMed database from 1985 to 2014, by continent and country distributions, ranked from the largest to the smallest number (within each continent distribution). Sakha Republic is one of the 10 autonomous Turkic Republics within the Russian Federation.

alone (143). Since numerous clinical NT case reports describe eosinophilia in the blood or CSF, the role of eosinophils in tissue larval killing and elimination is currently unclear.

Cerebral Vasculitis

A total of four cases of cerebral vasculitis are described in Table 2. However, only one case was documented by cerebral angiography, revealing multiple small branch occlusions in the middle cerebral artery, with multiple consecutive cerebral infarcts (144). In another case, Xinou et al. (118) detected cerebral infarction near cerebral granulomas. Cerebral vasculitis can develop during anthelmintic treatment, and whether infarctions are caused by a type IV (delayed) hypersensitivity to anthelmintic therapy or an acute inflammatory response to the antigen remains to be elucidated (118).

Myelitis

The effects of *Toxocara* larvae on the spinal cord have been reported repeatedly, and the injury is not limited to myelitis alone (125, 145) but is also concomitant with encephalitis or meningitis (146) (Table 2). Sellal et al. (147) described a young French woman presenting with recurrent myelitis. Eosinophilia and anti-*T. canis* IgG antibodies were detected in serum and CSF, and VLM was suspected. There was a good response to treatment with diethylcarbamazine. Another report concerned a 21-year-old Japanese woman who had a history of dog ownership and presented with eosinophilic meningoencephalomyelitis manifesting as epilepsy, pyrexia, frontal headache, ataxia, pleocytosis, and meningeal irritation (148). A T2-weighted MRI showed numerous hyperintense cortical and subcortical lesions. IgG antibodies against the *T. canis* antigen showed positivity in the CSF and serum. The manifestations were resolved successfully after treatment with diethylcarbamazine and corticosteroids. Furthermore, a 40-year-old Belgian woman presented with eosinophilic myelitis causing dermatomal dysesthesia and right leg weakness (148). Investigations revealed an elevated eosinophil count in the cerebrospinal fluid, and a spinal cord MRI showed abnormal hyperintensities. After treatment with mebendazole, the neurological abnormalities were resolved completely. In several meningomyelitis cases, MRI of the spine showed solitary or multiple hyperintense lesions on T2-weighted images, with strong homogeneous enhancement (125, 136, 146).

In a particularly unusual set of clinical cases, evidence for *T. canis* brain invasion was reported for patients who suffered from chronic Viliuisk encephalomyelitis (VE). VE is a neurological disease occurring only in the Sakha (Iakut/Yakut) population in Northeast Siberia (149). Goldfarb and Gajdusek (150) analyzed the phenotype and showed an acute phase with encephalitis and meningism progressing to a chronic pan-encephalitic syndrome. Clinical features of chronic VE consisted of ataxia, lower limb spasticity, predominant sensory gait apraxia, bladder dysfunction, and cognitive impairment. Most patients suffered an acute phase with meningitis-like symptoms before the chronic phase, and laboratory investigations showed a short-lived eosinophilia in the acute phase. In addition, eosinophilic infiltrations were confirmed through histological analyses of brain specimens from subacute/subchronic VE patients, which suggested an eosinophilic meningitis (150).

Recently, Storch and colleagues (151) used clinical, neuroimaging, and serological data in a cross-sectional study of 20 patients suffering chronic VE to explore hypotheses relating to the pathophysiology and cause of chronic VE. The clinical phenotype of chronic VE patients consisted of dementia in 57% of patients, urge incontinence in 70%, dysarthria in 80%, lower-limb spasticity in 90%, gait apraxia in 95%, and sensory ataxia in 100% of patients. Two-thirds of patients had acute-onset meningitis with cranial nerve deficits which subsided over the disease course. Blood hematology data were retrospectively analyzed from controls and chronic VE patients, revealing that in the subacute/acute phase, 65% of patients had transient, moderately to mildly raised eosinophils, compared to 0% of controls. The discovery of acute-phase eosinophilia prompted the investigators to consider neurotropic infectious agents linked to eosinophilic meningitis, such as viruses (varicella-zoster virus, rubella virus, measles virus, herpes simplex viruses 1 and 2 [HSV-1 and -2], cytomegalovirus, tick-borne encephalitis virus [FSME], and lymphocytic choriomeningitis virus

[LCMV]), bacteria (such as *Borrelia burgdorferi* and *Treponema pallidum*), and nematodes (*T. canis* and *A. cantonensis*). Immunodiagnostic results were similar between VE patients and controls for various neurotropic bacteria and viruses, although a high prevalence of elevated antibody indexes (AIs) was found for HSV-1, HSV-2, and varicella-zoster virus, though this was considered unlikely to be a specific cause of VE and was attributed to endemic infection (152).

In contrast, 70% of chronic VE patients had anti-*T. canis* antibodies, compared to 13% of controls (no difference was found for *A. cantonensis*). Although Storch and colleagues (151) claimed that chronic VE was triggered by eosinophilic meningitis, which might have been caused previously by *T. canis* infection, definitive proof of this relationship is still lacking. Nevertheless, the evidence published by Storch et al. (151) at least provided the first indication that Viliuisk encephalomyelitis is perhaps an endemic form of rare cerebral complications combined with cerebral and myelonic symptoms of *Toxocara* sp. infection; however, further parasitological exploration within the Viliuiski area is warranted in order for a comprehensive elucidation to be made.

Seizure

Seizures are paroxysmal events resulting from excessive, hypersynchronous electrical discharge of neurons causing a number of behavioral and clinical manifestations, e.g., dramatic convulsions. Recent advances in experimental neuroscience have revealed that inflammation can facilitate seizures or sustain seizure activity. Neuroinflammation occurs in the epileptic brain and can intensify seizures or increase seizure frequency, because neuroinflammation may directly affect neurovascular and glial function. Moreover, the effects of systemic inflammation can be mediated or facilitated by a loss of BBB function due to activation of circulating leukocytes and release of molecular mediators that increase vascular permeability (153).

It is estimated that 65 million people are affected by epilepsy worldwide, particularly in sub-Saharan Africa (SSA), whereas specific seizure-causing parasitic infections are largely absent in industrialized countries (154). Early reports have suggested that people with epilepsy (PWE) have a high rate of exposure to *T. canis* (155, 156). Woodruff et al. (155) found that a higher percentage of PWE (7.5%) reacted positively to a toxocariasis skin test than the case for apparently healthy controls (2.1%). They also found that a positive skin test in PWE was significantly associated with exposure to dogs. Arpino et al. (157) conducting a case-controlled study of more than 300 children and found a significant relationship between seizures and a positive serum reaction to *T. canis* antibodies. The relationship was strongest in children under the age of 5 years.

Owing to an improved specificity and sensitivity of serodiagnosis, the association between *T. canis* seropositivity and epilepsy was further investigated in various populations and suggested that toxocariasis may be a cofactor in the occurrence of epilepsy in areas where the helminth is endemic (70, 158). A large, case-controlled, cross-sectional study across five SSA countries found that risk factors for active convulsive epilepsy in children included head injury and difficulties in crying, breathing, or feeding after birth. In adults (≥18 years), epilepsy risk factors included malaria or pyrexia, exposure to *T. gondii*, *Onchocerca volvulus*, *Taenia solium*, or *T. canis*, and hypertension (73). A meta-analysis and systematic review of available data, including seven case-control studies, provided 1,867 subjects, including 1,017 people without epilepsy (PWOE) and 850 PWE, at ages ranging from 1 year to 17 years, while children below 10 years of age were excluded from one study (72). The studies were undertaken in Bolivia, the United States, Turkey, Italy, Tanzania, and Burundi, in urban and rural settings, to evaluate the relationship between epilepsy and *T. canis* seropositivity. The findings of these studies supported the existence of a positive association between *T. canis* seropositivity and epilepsy.

Recently, Kamuyu et al. (159) investigated the association between epilepsy and parasitic infections at five SSA sites. Their findings also revealed an association between exposure to *T. canis* as well as elevated levels of *T. canis* antibodies and the prevalence of active convulsive epilepsy. One major limitation concerning these various studies is the heterogeneity in the immunodiagnostic techniques employed, i.e., WB or ELISA. In addition, Kamuyu et al. (159) mentioned that a commercial kit which was employed to detect serum anti-*T. canis* IgG antibodies by using TESELISA had a 97% sensitivity and 78.6% specificity. Even though Quattrocchi et al. (72) stipulated that TESWB has a reasonable sensitivity and superior specificity compared to commercial or in-house TESELISA, it remains unavoidable that cross-reactivity will be caused by other soil-transmitted helminths with this assay. This limitation has already been revealed, i.e., sera from individuals with intestinal helminthiasis, e.g., ascariasis, trichuriasis, or schistosomiasis, can also cross-react with TES antigens as assessed by TESWB (160).

However, the evidence outlined above for an association between epilepsy and *T. canis* seropositivity does not prove causality between epilepsy and infection with *T. canis*. For causality to be definitively established, it is necessary to show that exposure to *T. canis* occurred before the onset of epilepsy. Although evidence is accumulating to suggest that infection with *T. canis* is implicated in epilepsy (71, 72), the exact etiological connection still requires more comprehensive investigation, i.e., the association needs to be established in cases where epilepsy has just developed (161), especially in regions where *Toxocara* occurs sympatrically with other epilepsy-causing infections (50).

Schizophrenia

Schizophrenia is a severe, debilitating mental disorder with devastating impacts on patients, their families, and society (162). Schizophrenia is a heterogeneous disorder characterized by a range of clinical features, such as positive symptoms, referring to psychotic behaviors, including hallucinations, and negative symptoms, associated with disruption of normal behavior, such as lack of motivation. The prevalence of schizophrenia has been reported to be 1% of the adult population, with development in late adolescence or early adulthood, and most patients suffer from the disease throughout their lifetime (163). Cognitive deficits affect sensory processing, episodic memory, processing speed, attention inhibition, working memory, and language and executive functions (164).

The invasion of the CNS by *T. canis* larvae may result in psychiatric and neurological disorders that could contribute to schizophrenia. However, compared to the case for *Toxoplasma*, the link between schizophrenia and *T. canis* infection has received much less attention (165). According to the "original dopamine hypothesis," hyperactive dopamine (DP) transmission is responsible for schizophrenic symptoms. Carlsson and Lindqvist (166) devel-

oped the hypothesis after demonstrating DP's role as a neurotransmitter. DP is produced in several areas of the brain, including the ventral tegmental region, prefrontal cortex, striatum, substantia nigra, and hippocampus, and changes in DP are linked to schizophrenia (167).

Positive symptoms, such as delusions and hallucinations, result from an excess of DP in the subcortical region, which hyperstimulates D2 receptors and is thought to result from disruption of the cortical pathway. Negative symptoms include anhedonia (loss of the capacity to experience pleasure) (97), lack of speech, and lack of motivation resulting from reduced prefrontal cortex D1 receptor stimulation (168). The "revised dopamine hypothesis" proposes hyperdopaminergia in the mesolimbic pathway and hypodopaminergia in the prefrontal cortex in patients with schizophrenia (169). In particular, hippocampal dysregulation of the DP system occurs in schizophrenia patients (169).

Using a murine model, Othman et al. (170) found that DP levels significantly decreased over time in the brains of mice infected with *Toxocara* larvae. In contrast, another study found enhanced expression of tyrosine hydroxylase (TH), which is capable of catalyzing the conversion of the amino acid L-tyrosine to L-3,4-dihydroxy-phenylalanine (L-DOPA), a precursor for DP (171; Fan et al., unpublished data). TH is present in the adrenal medulla, the peripheral sympathetic neurons, and the CNS (171). Substantial studies have indicated that an alteration of TH activity is related to disorders such as Parkinson's disease and schizophrenia (172). However, the role of the DP system in a schizophrenia disorder in NT remains to be elucidated comprehensively.

Di Fiore et al. (173) investigated the seroprevalence of *T. canis* infection in 335 Italian human sera and found a prevalence of 13% among psychiatric patients, compared with 9.4% of farmers, 1.9% of children, and 1.2% of blood donors. Richartz and Buchkremer (75) reported a case of a German woman who tested positive for *T. canis* antibodies in the CSF and who had cognitive deficits and symptoms of depression. In Turkey, Kaplan et al. (174) found that 45 of 98 patients with schizophrenia had a higher seroprevalence of *T. canis* infection than healthy individuals (45.9% versus 2%). Furthermore, in Egypt, El-Sayed and Ismail (175) found that toxocariasis was detected at a higher rate in patients with schizophrenia disorder (23.3% [21/90 patients]) than in controls (2.2% [1/45 patients]). In Mexico, Alvarado-Esquivel (176) found IgG antibodies to *Toxocara* in 4.7% of 128 psychiatric patients, compared to 1.1% of 276 healthy controls.

In India, Khademvatan et al. (177) also found that patients with schizophrenia disorders had a statistically higher seroprevalence of *T. canis* infection than healthy individuals (14% [14/100 individuals] versus 4.3% [4/95 individuals]), and schizophrenic women and men did not differ in their *T. canis* seroprevalence. Meanwhile, Cong et al. (178) undertook a seroepidemiological investigation of infection with *T. canis* in Shandong Province in eastern China, and they also found an insignificantly higher seroprevalence in schizophrenia patients (14.0% [33/235 patients]) than in clinically normal subjects (13.1% [187/1,431 subjects]) and pregnant women (9.2% [91/990 subjects]). From this range of epidemiological studies with a wide geographical variation, we can postulate either that the greater prevalence of *Toxocara* in patients with psychiatric disorders than in controls reflects a role for *T. canis* infection in the etiology of psychiatric diseases or that psychiatric patients have a higher risk of infection due to abnormal behavioral changes, such as poor hygiene and self-care skills as well as a propensity to eat inappropriate things (175).

Substantial studies have indicated that people with *T. gondii* infection may be highly susceptible to schizophrenia development (165). Since infection with *T. canis* would increase the risk for *T. gondii* infection and vice versa (113), we cannot completely exclude the possibility that schizophrenia syndrome in *T. canis*-seropositive patients is truly triggered by *T. gondii* rather than *T. canis* infection. However, this is still unclear, since the studies mentioned above did not reveal the status of *T. gondii* infection among schizophrenia patients. Clearly, further research on the possible mechanistic relationship between *Toxocara* brain involvement and schizophrenia, depressive, and cognitive disorders is required.

Cognitive Deficits

Substantial studies have indicated a correlation between CNS inflammation and cognitive impairment in a number of neurological diseases, e.g., Alzheimer's disease (AD), because CNS inflammation has been confirmed to be implicated in the development of amyloid neuritic plaques, one of the hallmarks of AD (179, 180). The impact of *T. canis* infection on cognitive development in humans is sorely lacking, with very few clinical or population-based studies having examined the relationship between neuropsychological parameters and *T. canis* seropositivity (18, 181). Some clinical studies have described various cognitive deficits associated with infection, including a lack of developmental progress and speech (181), depressive symptoms and cognitive deficits possibly indicative of dementia (75), mental confusion and cognitive impairment (66, 182), impairments of mental fluency and short-term and working memory spans, and slowed information processing (2).

At the population level, Worley et al. (183) first reported an association between *T. canis* seropositivity and poor reading achievement, distractibility, and lower intelligence in kindergarten children, but the effects of social class were not considered in the analysis. Later, Marmor et al. (184) undertook neuropsychological tests on children aged 1 to 15 years and found significant cognitive deficits in *T. canis*-seropositive children compared with seronegative controls adjusted for race, socioeconomic status, and blood lead concentrations. Thereafter, Nelson et al. (185) evaluated cognitive function in children aged 1 to 4 years and identified lower mental development scores and IQ levels in *T. canis*-seropositive children; however, blood lead levels, which have been linked with cognitive impairment, were not assessed in these subjects (186).

Jarosz et al. (181) undertook a study of more than 200 students of 14 to 16 years of age in rural Poland. The authors investigated the relationship between toxocariasis and the students' physical fitness and developmental age, and they demonstrated that boys who were seropositive performed significantly worse academically than students who were seronegative. However, the authors acknowledged that behavioral factors increasing exposure to infection, such as more time spent playing outdoors instead of studying, could have explained the relationship.

In a significant advance, Walsh and Haseeb (187) sampled 3,949 children living in the United States, using data from the Third National Health and Nutrition Examination Survey (NHANES III; 1988–1994). They reported statistically lower cognitive scores on both the Wechsler Intelligence Scale for Children, Revised

(WISC-R), and the Wide Range Achievement Test, Revised (WRAT-R), for seropositive children than for children who were seronegative. This finding controlled for ethnicity, socioeconomic status, gender, infection with cytomegalovirus, blood lead levels, and rural residence. Nevertheless, the need for additional longitudinal data to elucidate an etiological relationship between diminished cognitive function and toxocariasis warrants further comprehensive investigations (187).

Data from murine models exploring the effect of *T. canis* infection on memory and learning are particularly relevant to human infection (18). Cox and Holland (188) used spatial learning tasks to assess information-gathering ability and memory in mice. Initial experiments utilized infected and control LACA mice. These were exposed to a particular resource, a water tube, in a novel environment to test the latency required for mice to relocate the resource after a period of deprivation, an indication of memory capacity in mice. Mice classified as having large and moderate numbers of larvae in the brain took longer to perform tasks than control mice and mice with low-level infections. The experiments were repeated using BALB/c mice, which are susceptible to *Toxocara* cerebral infection, and resistant NIH mice. BALB/c mice required significantly more time to complete tasks than NIH mice, suggesting the occurrence of memory loss, which may be attributable to where the larvae were located in the brain (189). Studies have reported larvae in the telencephalon (190) and cerebellum (191), both of which are regions of the brain linked to memory and learning as well as control of voluntary movement and coordination.

Idiopathic Parkinson's Disease

Idiopathic Parkinson's disease (IPD) is a common neurodegenerative disorder characterized by a progressive degeneration of midbrain dopamine neurons of the substantia nigra, resulting in a variety of motor symptoms, e.g., rigidity, akinesia, and resting tremor. The molecular pathways leading to clinical alterations require comprehensive elucidation but may be the result of either environmental factors, genetic influences, or a combination of these (192). Degeneration of neurons in IPD may result from several pathogenic mechanisms, including neuroinflammatory processes, oxidative stress, excitatory amino acids, mitochondrial abnormalities, elevated intracytoplasmic free calcium, apoptotic processes, and cytokines. Recently, studies have suggested a fundamental role for microglia-driven neuroinflammation and the neurotoxic products (nitric oxide, proinflammatory cytokines, and reactive oxygen species) of infiltrated peripheral immune cells in the pathological process of IPD (193). The impact of infectious agents on IPD patients and the relationship between infections and pathogenesis or clinical findings for IPD are unclear. A few studies have indicated that infectious agents, e.g., influenza virus, may play a role in IPD (194).

T. canis larval invasion into the CNS may cause neurological manifestations resulting in some neurological and psychiatric disorders that may include IPD; however, a potential relationship between infection with *T. canis* and IPD has received little attention. The primary symptoms of IPD result from a greatly reduced activity of DP-secreting cells caused by a loss of cells in the substantia nigra pars compacta, thus possibly leading to insufficient formation and activity of DP produced in certain neurons within parts of the midbrain (192). Recently, Çelik et al. (195) found that although the *T. canis* infection seroprevelance was higher in IPD patients (6.0%) than in controls (0%), no statistical difference was found in the seropositivity rate between IPD and control groups.

Using a murine model, Othman et al. (170) found that mice infected with *Toxocara* showed increased gene expression of nitric oxide and proinflammatory cytokines, particularly in the chronic stage. While proinflammatory cytokines are neuroprotective, prolonged or elevated levels can cause neuronal damage (170). In particular, compared with uninfected mice, *T. canis*-infected mice showed significant decreases in DP, monoamine, GABA, and serotonin levels. In contrast, as discussed in "Schizophrenia," above, our study found that DP expression increased in the brains of *Toxocara*-infected outbred ICR mice (Fan et al., unpublished data). This difference in DP expression between two animal studies warrants further investigation to further elucidate the possibility of DP-related IPD occurring with neurotoxocariasis.

Dementia

The causes of dementia, a decline in cognitive function severe enough to affect social or occupational functioning, are complex and may be due to AD or vascular dementia (196). The pathogenesis of dementia is postulated to be very similar to that of cognitive dysfunction (196), indicating that CNS inflammation is implicated in this neurodegenerative disease due to the development of amyloid neuritic plaques (179, 180).

Higher *T. canis* seroprevalences have been found for various patient groups with neuropsychiatric disorders, e.g., seizure, cognitive deficits, IPD, and schizophrenia, than for control groups (159, 175, 187, 195); however, clinical case reports concerning the status of *T. canis* infection among dementia patients are rare. Among the cases shown in Table 2, only one NT patient who exhibited dementia and depression was reported (75). In this case, a 65-year-old woman with a long history of cognitive decline and depression was described. Laboratory examination revealed eosinophilia as well as reactive antibodies against *T. canis* antigen in the CSF. The infection was possibly attributable to her occupation as a shepherdess, with a high frequency of close contact with dogs. Cognitive deficits were improved by treatment with albendazole.

Nevertheless, dementia cases caused by *T. canis* are rarely reported and may be overlooked due to the fact that most humans with cerebral toxocariasis do not present significantly clinical neurological signs as a consequence of light parasitic burdens (18). This, along with the longevity of *T. canis* larvae resident in the internal organs, including the brain (20), demonstrates the need for more extensive investigation of the link between dementia and NT. A summary of potential linkages between *T. canis* infections and neuropsychiatric disorders is shown in Table 3.

MURINE MODELS OF NEUROLOGICAL INFLAMMATION, UBIQUITIN-PROTEASOME IMPAIRMENT, AND COGNITIVE DEFECTS IN CEREBRAL TOXOCARIASIS

Humans are known to harbor *Toxocara* larvae in their brains, but the number of cases of cerebral infection described in the literature is still small. Additionally, the cryptic nature of the effects of brain involvement are not easily explained or observed in humans with CT. The choice of an appropriate animal model to explore the behavioral and pathological implications of cerebral toxocariasis is therefore important. Furthermore, our and other researchers' experience of methodological and ethical challenges associated with studies of geohelminth infections and cognitive development in human subjects (197) highlights the necessity of

TABLE 3 Potential linkages between *T. canis* infections and neuropsychiatric disorders

Neuropsychiatric disorder	Possible mechanisms	Type of studies	Possible causal relationships	References
Seizure	Increased proinflammatory cytokine expression and BBB dysfunction	Human/animal studies	Three large-scale studies provided evidence for a positive association between *T. canis* seropositivity and seizure.	71–73, 153–159, 200, 208
Schizophrenia	Increased or decreased dopamine expression	Animal studies	Epidemiological studies indicated that the schizophrenia group had a higher seroprevalence of *T. canis* infection than healthy individuals. Increased or decreased dopamine expression was observed in the *T. canis*-infected mouse brain.	97, 166–170, 173–178
Cognitive deficits	CNS inflammation causes amyloid neuritic plaque formation	Human/animal studies	Several epidemiological studies indicated significant cognitive deficits in *T. canis*-seropositive children compared with seronegative controls.	170, 179–189, 199
Idiopathic Parkinson's disease (IPD)	CNS inflammation causes dopaminergic neuronal degeneration	Animal studies	Insignificantly higher seroprevalence of *T. canis* infection in patients with IPD than in controls. Significantly decreased GABA and DP levels were found in *T. canis*-infected mice compared with uninfected mice.	170, 192–195
Dementia	CNS inflammation causes amyloid neuritic plaque formation	Human studies	An elderly German woman with a long history of depression and cognitive decline showed reactive antibodies against *T. canis* antigen in CSF.	75, 179, 180
Alzheimer's disease	CNS inflammation causes amyloid neuritic plaque formation	Human/animal studies	Significantly increased proinflammatory cytokines and insoluble β-amyloid levels were found in brains of *T. canis*-infected mice compared with uninfected mice.	170, 196, 200, 208

useful laboratory animal model systems to investigate the relationship between learning deficits and cerebral toxocariasis. Holland and Hamilton (18) outlined the advantages of mouse models for toxocariasis, including ease of manipulation and larval detection in small organs, the selective choice of inbred or knockout strains, and, importantly, the role of *Mus musculus* and other small rodents in the natural *Toxocara* life cycle under field conditions.

The mouse model has been useful for exploring the impact of *Toxocara* infection on murine behavior. Infected mice tend to be less explorative and active and less responsive to novelty, and they show lower levels of aversion to predator stimuli and open areas than control animals (188, 198). These abnormal behavioral changes are likely related to the site where *T. canis* larvae are located in the brain, the immune response directed against *T. canis* larvae, and, more importantly, pathological effects rather than parasite-altered host behavior (199). Therefore, mice are useful animal models for exploration of the impact of *T. canis* on the biology of the brain and behavior as well as the pathogenesis of neurotoxocariasis.

Experimental work in mice has established evidence that may have implications for human health, such as the following: larvae recovered from the murine brain differ in number between genetically different inbred mice inoculated with the same dose (189), the distribution of larvae may not be random in the brain (190, 191), behavioral alterations are dose dependent (198), cerebral infection can lead to deficits in memory and learning (189), and infection in the brain induces an inflammatory immune response (82, 200). Given the central role of cytokines in the brain under normal or disease conditions, prolonged exposure to proinflammatory cytokines that promote neural injuries, e.g., tumor necrosis factor alpha (TNF-α), IL-6, and IL-1β, may aggravate neurodegenerative progression and compromise vulnerable neurons (201). Our knowledge of the systemic immune response to *T. canis* greatly exceeds that of the brain's immune response (202). Evidence from other brain-inhabiting parasites, such as those causing malaria (203), trypanosomiasis (204), toxoplasmosis (205), and neurocysticercosis (206), demonstrates that cytokines produced in response to neurotropic parasites can contribute to CNS diseases that often lead to pathological injuries in the brain.

Experiments conducted by Hamilton et al. (200) showed that *T. canis*-infected BALB/c mice exhibited significantly raised mRNA levels for IFN-γ, IL-5, IL-10, and inducible nitric oxide synthase (iNOS) compared to infected NIH mice. Furthermore, these levels were particularly raised at 35 and 42 days postinfection, times that coincide with observed behavioral alterations, most notably memory impairment. Dantzer et al. (207) proposed a "sickness behavior" that was triggered by proinflammatory cytokines involved in an array of behavioral symptoms, e.g., decreased exploration, reduced memory and learning, and depression of locomotor activity, in humans and mice. In particular, memory and learning impairments were linked to elevated levels of IL-1β, revealing an interference of memory storage by an increase in cytokine production. Moreover, Liao et al. (82) observed biomarkers (BIABs) associated with brain injury, including glial fibrillary acidic protein (GFAP), TGF-β1, S100B, tissue transglutaminases (tTG), AβPP, NF-L, and p-tau, in brains of ICR outbred *Toxocara*-infected mice given a single-dose inoculation of 250 eggs. They also observed injury to the BBB in a similar cerebral toxocariasis experiment, as assessed by pathological changes,

GFAP expression, and Evans blue (EB) dye concentration. In addition, abnormal BBB permeability and cerebral injury increased over the duration of the infection, though the changes appeared to be unrelated to larval numbers in the brain (208).

The issue of infective dose and the resultant larval burden (and the relationship between observed behavioral and immunological changes) in the brain for murine animal models is an important one. In contrast to Hamilton et al. (189, 200), who utilized doses of 1,000 ova, Fan et al. (209) used a single dose of 250 *T. canis* eggs to infect ICR outbred mice and reported larval recovery rates ranging from 2.9% to 3.8% from the murine brain. This larval recovery is close to that of 4.4% recorded by Cox and Holland (188), who used an inoculum of 100 ova given to outbred LACA mice. Good et al. (190) assessed the larval distribution in the brains of CD1-ICR outbred mice, and they found that brain region and dose were significant factors contributing to the observed distribution. Cox and Holland (188) suggested that the provision of a low-dose inoculation, with a resultant low *T. canis* larval burden, more realistically reflects cerebral toxocariasis infection in wild rodents and humans.

These observations underline an urgent need to further elucidate the link observed between enhanced BIAB expression or abnormal BBB permeability and behavioral alterations in experimental cerebral toxocariasis. Liao et al. (82) also indicated that enhanced expression of BIABs, which may be deleterious to the brain, might be explained by a ubiquitin-proteasome system (UPS) dysfunction that is unable to degrade misfolded, damaged, or unwanted proteins with the potential to form toxic aggregates in the brains of mice infected with *T. canis*. It has been hypothesized that the presence of deposits consisting of ubiquitylated proteins in diseased neurons (found in many hereditary and sporadic neurodegenerative diseases) is suggestive of a link between pathogenesis and UPS dysfunction, e.g., in AD (210), and whether cerebral infection by *T. canis* has damaging effects that increase the risk of cerebral toxocariasis progressing to neurodegenerative disorders should not be completely disregarded.

Furthermore, Othman et al. (170) showed that elevations of proinflammatory cytokines, such as iNOS, TNF-α, and IL-6, as well as changes in neurotransmitter profiles in *T. canis*-infected mouse brains were greatest during chronic infection, as indicated by enhanced GFAP expression. Of particular importance was their novel observation that the normal patterns of neurotransmitters, e.g., GABA, dopamine, and serotonin, were disrupted as a result of *T. canis* infection. Since changes in neurotransmitter patterns in humans are related to a variety of perturbations, including behavioral disturbances and seizures, these observations, along with those on enhanced proinflammatory cytokine expression, could provide explanations for the cognitive and behavioral deficits seen in CT in mice and humans (170) (Table 3).

CEREBRAL TOXOCARIASIS VERSUS ALZHEIMER'S DISEASE: A SILENT PROGRESSION

AD is the most common form of dementia worldwide. Two major neuropathological hallmarks characterize the condition: extracellular plaques largely consisting of insoluble beta-amyloid (Aβ) peptide aggregates and the presence of intracellular neurofibrillary tangles (NFTs) comprised of the hyperphosphorylated form of microtubule-associated protein tau (211). Animal and clinical studies have indicated that insoluble $A\beta_{42}$ peptide accumulation is crucial for development of AD; this is thought to derive from aberrantly processed or overproduced AβPP, and dysregulation of AβPP production may be important in the etiology of Alzheimer's disease (211). Generation of the soluble $A\beta_{40}$ peptide or insoluble $A\beta_{42}$ peptide requires sequential cleavages of AβPP. Extracellular cleavage by beta-secretase 1 (beta-site AβPP-cleaving enzyme 1 [BACE 1]) leaves a membrane-bound fragment, referred to as AβPP-C99, and a large soluble extracellular fragment. Cleavage of AβPP-C99 within its transmembrane domain by γ-secretase releases the intracellular domain of AβPP and produces the insoluble $A\beta_{42}$ peptide, which is the primary etiology of AD. In contrast, α-secretase cleaves AβPP closer to the cell membrane than BACE1 does, resulting in production of the soluble $A\beta_{40}$ peptide, which may be removed from the brain (211). NFTs are made up of paired helical filaments (PHFs); tau in these PHFs is abnormally phosphorylated (212).

In addition to hypotheses about the Aβ cascade and tauopathy, the pathological mechanism of AD is complicated and remains unclear; however, some cytokines, i.e., TGF-β1 (213) and S100B (214), glial proteins, i.e., GFAP (215) and NF-L (216), and enzymes, i.e., tTG (217) and ubiquitin (210), have been characterized as being highly associated with or involved in not only acute injury of cerebral toxocariasis but also AD. In particular, TGF-β1, a multifunctional cytokine, plays a significant role in regulating brain responses to inflammation and injury, and experimental and clinical studies have indicated that it is highly involved in initiating or promoting amyloidogenesis (218, 219).

Under normal circumstances, S100B promotes neurite outgrowth, stimulates proliferation of astroglial cells, and increases intracellular concentrations of free calcium in astrocytes and neurons. It has been reported that overexpression of S100B may have deleterious consequences, including dystrophic changes in neurons and neuritis, which characterize the neuritic Aβ plaques used in AD diagnosis (220). Some intermediate filament proteins, such as GFAP and NFs, have also been proposed to be associated with AD. In CNS injury, elevated expression of GFAP was associated with astrocyte activation, modulated by TGF-β1, during neural responses to injury (221). NFs, which are comprised of neurofilament light (NF-L), neurofilament medium (NF-M), and neurofilament heavy (NF-H) subunits, are intermediate filaments found specifically in neurons and are considered to convey tensile strength, structural rigidity, and intracellular transport guidance to dendrites and axons, while abnormal accumulation of NF-L is detected in AD (216, 222). Evidence also indicates that some enzymes, such as tTG and ubiquitin, are potent mediators of the pathogenesis of AD. By facilitating the formation of one or both of two insoluble neurotoxic proteins, Aβ and tau, tTG may be involved in AD pathogenesis (211). The UPS functions in cellular quality control by degrading misfolded, unwanted, or defective proteins. The UPS also serves as the primary route for degradation of thousands of normal short-lived and regulatory proteins and thus contributes to the regulation of a variety of cellular processes. Failure to detect and eliminate misfolded proteins, or the UPS itself, may contribute to or be a target for toxic proteins involved in the pathogenesis of neurodegenerative diseases, including AD (223). Elevated accumulation of the insoluble $A\beta_{42}$ peptide is considered to compromise neuronal function and viability through dysregulation of intracellular Ca^{2+} homeostasis and impairment of mitochondrial activity and to stimulate proapoptotic signaling through interaction with neuroreceptors. The increased activation of kinases results in dendritic spine loss, tau hyperphospho-

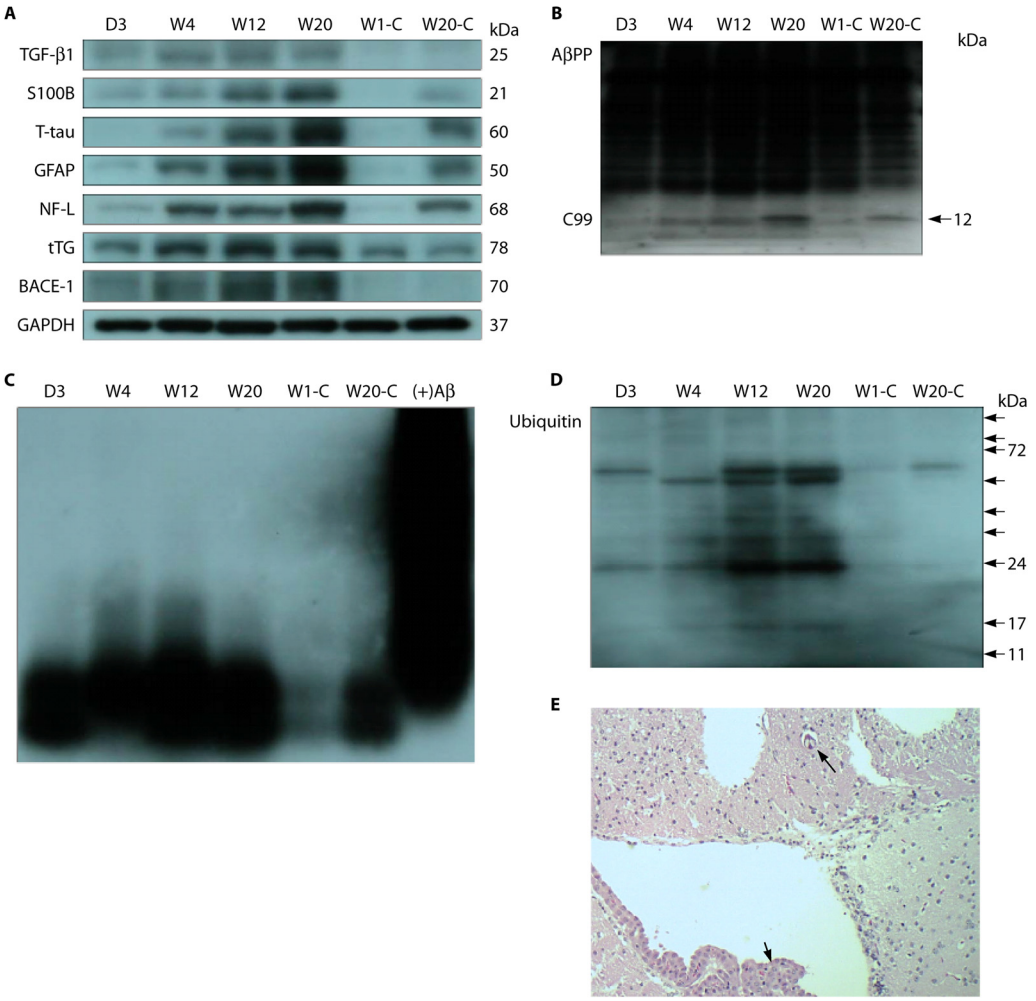

FIG 3 Increased expression of Alzheimer's disease-associated neurodegenerative proteins, including TGF-β1, S100B, T-tau, GFAP, NF-L, tTG, and BACE1 (A), β-secretase-derived AβPP fragment C99 (AβPP-C99) (B), and β-amyloid peptides of 42 amino acids ($Aβ_{42}$) (C), and UPS dysfunction (D) in the brains of *Toxocara canis*-infected mice inoculated with a single dose of 250 infective eggs, at 3 days (D3), 4 weeks (W4), 12 weeks (W12), and 20 weeks (W20) postinfection, as assessed by Western blotting. (E) *T. canis* larva (longer arrow) found in an area close to the choroid plexus (shorter arrow) at 12 weeks postinfection. GAPDH, glyceraldehyde-3-phosphate dehydrogenase; W1-C and W20-C, uninfected control mice at 1 week and 20 weeks postinfection; (+)Aβ, the $Aβ_{42}$ peptide was run by SDS-PAGE and then transferred to the membrane, and it was recognized by a mouse anti-$Aβ_{42}$ monoclonal antibody which is regarded as a positive control. These data are our unpublished observations.

rylation, cytoskeletal compromise, and accumulation of NFTs. A number of factors are released by damaged neurons and induce the generation of free radicals and inflammation, whose effects are intensified by proinflammatory cytokine release (224).

Our preliminary data showed that *T. canis*-infected ICR outbred mice exhibited significant expression of biomarkers associated with AD, such as GFAP, total Tau (T-tau), TGF-β1, TG2, S100B, and NF-L, with 2- to 4-fold increases in the brain compared to the levels in age-matched uninfected controls at 20 weeks postinfection. BACE1, AβPP-C99, and $Aβ_{42}$ were observed to have 3- to 13-fold, 3- to 3.5-fold, and 3- to 5-fold increases, respectively, within the brains of mice infected with *T. canis* compared to age-matched uninfected mice at 20 weeks postinfection (Fig. 3A to C).

UPS dysfunction initially occurred early, at 3 days postinfection, became abnormal at 4 weeks postinfection (Fig. 3D), and then continued until 20 weeks postinfection (Fig. 3D). Pathological findings indicated that one *T. canis* larval section was found in an area close to the choroid plexus (Fig. 3E). It seemed probable that AD-associated protein aggregation caused the dysfunction of the UPS, as a number of studies have proposed that intracellular deposition of ubiquitylated and aggregated proteins, as well as an increase in ubiquitin, is a cytopathological aspect of AD (225, 226), and this was confirmed by direct impairment of UPS function caused by aggregation of proteins (223). The animal use protocol in this experiment was reviewed and approved by the Institutional Animal Care and Use Committee, Taipei Medical University (approval no. LAC-99-0010). All animal experiments were carried out in accordance with institutional policies and guidelines for the care and use of laboratory animals, and all efforts were made to minimize animal suffering. Taken together with our previous study that revealed the impairment of the BBB in murine brains invaded by *T. canis* larvae (208), these preliminary, unpublished results provide fresh insights to better understand the possible role of *T. canis* larval in-

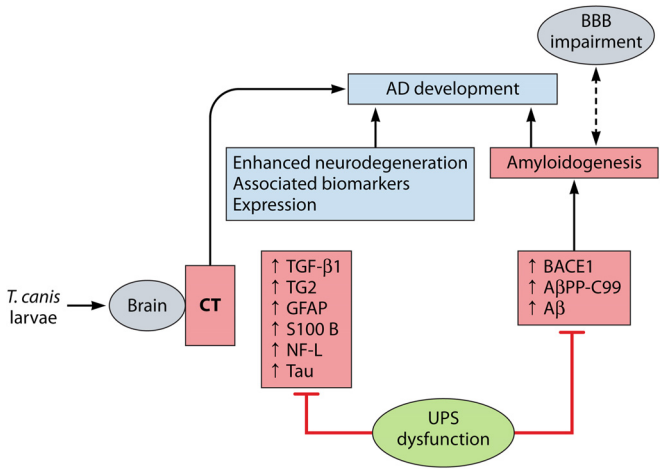

FIG 4 Illustration of the hypothesis that cerebral toxocariasis may progress to Alzheimer's disease.

vasion in the potential development of AD due to enhanced AD-associated neurodegenerative biomarker expression.

CONCLUSIONS

Based upon the high levels of exposure to *Toxocara* worldwide but the relatively small numbers of human cerebral toxocariasis cases reported in the literature, most cases of human toxocaral brain involvement are likely to involve small numbers of larvae that do not present with significant clinical neurological signs. However, experimental data obtained from monkeys (227) and mice (228) confirm that *T. canis* larvae may accumulate in the brain and remain there for extended periods. This longevity may contribute to cerebral pathogenesis, and clinically, cerebral toxocariasis patients do indeed present with various neuropsychiatric disorders, e.g., seizure, cognitive deficits, and, rarely, dementia. Epidemiological observations also find a higher seroprevalence of *T. canis* in patients with schizophrenia and IPD than in controls.

However, for ethical and methodological reasons, the complex relationship between cerebral toxocariasis, neuropathogenesis, and observed behavioral deficits needs to be explored in a suitable animal model in order to definitively outline the mechanistic relationships. Care needs to be exercised in controlling for potential confounding variables in murine models, such as genetic status, infective dose, duration of infection, refinement of behavioral testing, and the challenge of measuring behavioral alterations in tandem with complex pathophysiological, biochemical, and immunological measures (18).

Our preliminary data from a murine model hypothesize that cerebral toxocariasis may exhibit a silent progression to AD (Fig. 4). Certainly, the enhanced expression of GFAP indicates that the very few *T. canis* larvae that had migrated to the brains of ICR outbred mice fed a low dose of infective ova were capable of causing brain injury (82, 208). Furthermore, BBB impairment (208) and UPS dysfunction can occur simultaneously in mice with cerebral toxocariasis. The expression of AD-associated biomarkers also significantly increased with infection duration, and in addition, expression of BACE1, AβPP-C99, and $A\beta_{42}$ (which represent apparent amyloidogenesis), which is also believed to be an important cause of AD, was enhanced in mice with cerebral toxocariasis (Fig. 4). We thus postulate that cerebral toxocariasis may progress to AD due to an impaired UPS that cannot degrade the unwanted or nerve-deleterious proteins, e.g., AD-associated proteins. Combined with a compromised BBB, the UPS cannot perform its normal function to balance the cerebral environment by transporting harmful molecules out of the brain, thus leading to nerve-deleterious materials accumulating in the brain and the disease gradually progressing to AD (229). To conclude, the underlying molecular pathogenesis associated with cerebral toxocariasis that may progress to AD is complex; however, we provide an animal model and a hypothesis to further elucidate the possible pathogenic mechanism.

APPENDIX

DEFINITIONS

Aβ β-Amyloid
AD Alzheimer's disease
AβPP β-Amyloid precursor proteins
BACE1 Beta-site AβPP-cleaving enzyme 1
DP Dopamine
DUSN Diffuse unilateral subacute neuroretinitis
GFAP Glial fibrillary acidic protein
IPD Idiopathic Parkinson's disease
L-DOPA L-3,4-Dihydroxyphenylalanine
NF-L Neurofilament light chain
NFTs Neurofibrillary tangles
NLM Neural larva migrans
TGF-β1 Transforming growth factor β1
TH Tyrosine hydroxylase
tTG Tissue transglutaminases
UPS Ubiquitin-proteasome system
VE Viliuisk encephalomyelitis

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Chia-Kwung Fan received his Ph.D. from the Graduate Institute of Microbiology, National Taiwan University College of Medicine. Currently, he is working as a full-time Professor in the Department of Molecular Parasitology and Tropical Diseases, School of Medicine, Taipei Medical University, and he also works as an Expert Consultant for the Centers for Disease Control, Ministry of Health and Welfare, Taiwan. His current administrative job is as Department Chair. His research has included the study of zoonotic parasitoses, particularly the epidemiology, molecular pathogenesis, and immunopathogenesis of toxocariasis and toxoplasmosis, since 1990. Since 2009, he has led his research team to undertake epidemiological investigations with associated risk factor analysis of *T. canis* infection among school children in Africa (Swaziland and Sao Tome and Principe) as well as the Republic of Marshall Islands. He has authored 54 research articles from 2003 to the present, as well as 3 book chapters.

Celia Holland, B.Sc., Ph.D., M.R.I.A., is a Professor of Parasitology at Trinity College Dublin. Her main research interests are in the epidemiology and control of the soil-transmitted helminths, including *Ascaris* and *Toxocara*. She was elected to the Fellowship of Trinity College and as a member of the Royal Irish Academy in recognition of her research. Professor Holland is an Invited Expert on the WHO Advisory Panel on Parasitic Diseases and is currently Secretary General of the European Federation of Parasitology. She is an Editor of the journal *Parasitology*. She is the author of 108 publications, including peer-reviewed journal articles, books, and book chapters on parasitology and related topics, including the senior editorship of *Toxocara: the Enigmatic Parasite* and *The Geohelminths: Ascaris, Trichuris and Hookworm*, as part of the *World Class Parasites* series. In 2013, she was the sole editor of a book entitled *Ascaris: the Neglected Parasite*, published by Elsevier.

Karen Loxton received a B.Sc. in ecology from University College Cork and received her Ph.D. from Trinity College Dublin. Her current research interests involve the role of parasites in species invasions, particularly those of small mammals.

Ursula Barghouth obtained her M.S. in public health from the School of Public Health and Tropical Medicine at Tulane University in 2012, with a focus on tropical medicine and parasitology. She conducted her practicum at the Taipei Medical University Department of Parasitology under the supervision of Ted Fan, with a focus on inhibition of inflammatory mediators to lessen pulmonary injury caused by *T. canis*. She is currently a student at the A. T. Still University School of Osteopathic Medicine in Arizona, obtaining her medical degree and a second master's degree, in health administration.