Parasites on the brain?

Abi Chase

I have a snow globe filled with ticks on my desk. Once you get over the disgust, it is fascinating to shake and admire the repulsive bodies floating slowly down, all of their legs intermingling as they form a mat on the bottom. Veterinarians commonly encounter parasites, and controlling them is a large part of our job. But I appreciate that for our medical colleagues, thankfully, this is not the case. Oh, but if only life was that simple!

There are, at least, a couple of parasites that are silently prevalent in the human New Zealand population. You will not see wriggling worms or microscopic crawlies, but you may see asthma, neuropsychiatric disorders, road traffic accident injuries and children with reduced cognitive function. Two parasites of particular concern are *Toxoplasma gondii* and *Toxocara cati/canis*. This article will focus solely on the latter, as my admiration for parasites was recently called into question when I reviewed an article on this worm. What I read made me go home, worm all of the animals in my house, research what I could medicate my children with (obviously not advised—this was done in panic) and now has me picking up other people's dog poo. That is not to dismiss *Toxoplasma gondii* and its ability to alter human behaviour (increased risk taking leading to higher road traffic incidents) and dictate the sex of your child. But that will have to wait for another time.

One Health

The lives of humans and animals are interconnected in deep and complex ways. Over three quarters of the emerging human infectious diseases are zoonotic (Kshitiz et al 2018). With two separate busy professions overseeing the health of humans and animals, collaboration is difficult to achieve. The advantages, however, can be significant.

One Health attempts to break down residual barriers between human, veterinary and environmental health professionals and to build interdisciplinary teams that simultaneously work to maximise outcomes for all. The field of parasitology is an excellent example of where this approach is particularly beneficial.

Human toxocariasis

Research has been emerging over the past few years associating human toxocariasis (HT), caused by the dog and cat parasites *Toxocara canis/cati*, with a variety of human disease (Ma et al 2018) and it is a significantly underdiagnosed public health issue around the world (Ma et al 2018; Rostami et al 2019). HT can cause a wide range of disease, such as childhood asthma (Momen et al 2018), urticaria (Vinas et al 2020), neuropsychiatric disorders (Fan 2020) and decreased cognitive function in children and young adults (Walsh and Haseeb 2012; Erickson et al 2015). It has also recently been associated with increased tumour size in mice used as human models in mammary tumours (Ruiz-Manzano et al 2020).

However, HT is rarely on a differential list, particularly where clinical signs in children are as non-descript as fever, abdominal pain, nausea and wheezing (Magnaval et al 2001) and is, therefore, rarely diagnosed (Ma et al 2018).

The parasite

Toxocara canis/cati are ascarid parasites that inhabit the small intestine of canids/felids. They are relatively non-pathogenic unless present in large numbers in puppies and kittens. Definitive hosts shed *Toxocara* eggs into the environment with their faeces. These eggs are unembryonated when laid and thus not immediately infective.

Development of the infective third-stage larva inside the egg may require weeks to months, as this process is affected by temperature and humidity in the environment. *Toxocara* eggs may survive for up to four years in warm and humid environments (Deutz et al 2005).

Humans become infected by ingesting eggs containing infective larvae (eg, children eating soil/sand or raw vegetables), or the infectious larvae themselves, from ingestion of undercooked meats/offal of paratenic hosts (numerous and includes chickens and livestock). These larvae penetrate the intestinal wall and are transported to different tissues with the blood and lymphatic system. The resulting disease, toxocariasis (or toxocarosis), is one of the most reported zoonotic helminth infections worldwide (Rubinsky-Elefant et al 2010). It is considered by the US American Centres for Disease Control (CDC) as one of the five neglected parasitic infections with priority for public health action. The persistence of larvae in the brain, eye, liver and muscle can cause a broad range of clinical symptoms, which most often occur in children (Despommier 2003). There are four distinct syndromes: visceral larval migrans, common/covert toxocariasis, ocular larval migrans and neurotoxocariasis (summarised in Figure 1).

Visceral larval migrans

Visceral larval migrans (VLM) syndrome is a clinically apparent systemic form caused by a high infection dose or repeated exposure. The symptoms are presumably induced by an immediate hypersensitivity response to degenerating larvae in the affected tissues (Despommier 2003). Classical VLM is associated with various symptoms such as general malaise and fatigue, anorexia, fever and abdominal complaints attributed to hepatomegaly and splenomegaly, as well as shortness of breath, wheezing or coughing (Gillespie 1987; Carvalho and Rocha 2011). Severe VLM is relatively uncommon, whereas the mild VLM syndrome with less severe symptoms is frequent (Kayes 1997). VLM is associated with leukocytosis including high eosinophilia (Despommier 2003; Fan et al 2013) and many patients suffer from IgG/IgE hyper-γ-globulinaemia (Fan et al 2013; Maizels 2013).

Covert or common toxocariasis

Epidemiological surveys report a high *Toxocara* seroprevalence in many countries worldwide. However, only a small number of VLM cases have been described. This has led to the suggestion that a moderate variation of VLM exists, which was termed 'covert' or 'common' toxocariasis where infections remain asymptomatic or induce only mild or non-specific clinical signs, and thus often remain undiagnosed (Taylor et al 1987). The clinical diagnosis of covert toxocariasis is challenging as the disease comprises various combinations of non-specific symptoms including fever, weakness, lethargy, sleepiness, anorexia, headache, wheezing, abdominal pain, nausea, vomiting, behavioural disorders, pulmonary symptoms, limb pain, cervical lymphadenitis, hepatomegaly, pruritus and rash (Glickman et al 1987; Taylor et al 1987; Kayes 1997; Waindok et al 2021).

Ocular larval migrans

The ocular larva migrans (OLM) syndrome is characterised by larval invasion into the eye (Ashton 1960). The symptomatology of OLM is diverse, ranging from asymptomatic to severe. Migrating larvae induce an eosinophilic inflammatory immune response (Stewart et al 2005), which may be accompanied by marked vitritis, secondary cataracts and mild anterior chamber reactions (Sabrosa and de Souza 2001). The extent of eosinophilia determines the fibrotic granulomatous response, a strong clinical indication of OLM (Waindok et al 2021).

Neurotoxocariasis

The accumulation and persistence of *Toxocara* larvae within the CNS are termed cerebral or neurotoxocariasis (NT). In contrast to other tissues, larvae in the CNS are not encapsulated into granulomas, but their migratory tracks result in areas of necrosis and inflammatory infiltration with secondary granuloma formation (Pawlowski 2001; Abdel Razek et al 2011; Springer et al 2019). Overall, the pathogenesis of NT is complex and poorly understood compared to other forms of disease provoked by *Toxocara*. Diagnosis is challenging and the frequency of NT is probably underestimated (Hotez and Wilkins 2009; Holland and Hamilton 2013). NT is accompanied by eosinophilia in both blood and cerebrospinal fluid (CSF) (Finsterer and Auer 2007). Recruitment of eosinophilic granulocytes to the site of inflammation is a common hallmark of NT, and eosinophilic meningoencephalitis, eosinophilic meningitis and eosinophilic encephalitis are repeatedly recorded (Fan et al 2015). Furthermore, injury of the spinal cord due to migrating larvae can manifest as myelitis, Viliuisk encephalomyelitis, (meningo) encephalomyelitis, lower motor neuron disease and spinal abscesses (Fan et al 2015). *Toxocara* seropositivity has been linked to deficits in the development of speech as well as poor reading achievement, distractibility and lower intelligence in kindergarten children (Jarosz et al 2010; Walsh and Haseeb 2012). These cognitive dysfunctions and learning difficulties can lead to detrimental long-term consequences, especially in school children. NT has also been implicated as a possible cause of various neurological deficits and neuropsychological disorders. The association between seizures and a positive *Toxocara* serology supports the hypothesis of the parasite as a causative agent of epilepsy (Quattrocchi et al 2012). Moreover, larval invasion into the CNS may induce psychiatric and neurological disorders that could contribute to schizophrenia, possibly due to an effect on dopamine (Othman et al 2010). But the role of the dopamine system in NT remains to be elucidated comprehensively. The association between schizophrenia and *Toxocara* seropositivity was the focus of some studies and case reports published in the last decades, but the results remain contradictory (Cong et al 2014). Thus, it remains unclear whether *T. canis* infection may contribute to mentioned neurological diseases or if patients with neuropsychological disorders exhibit a higher risk of *Toxocara* infection due to abnormal behaviour (eg, a tendency to eat inappropriate things, and decreased self-care) (El-Sayed and Ismail 2012). Furthermore, *Toxocara* infection has been associated with mental confusion and cognitive impairments, possibly indicative of dementia (Richartz and Buchkremer 2002; Salvador et al 2010; Waindok et al 2021).

Prevalence

The worldwide prevalence of HT in healthy humans has recently been estimated to be 19%, increasing non-significantly over the last few decades and varying widely between countries (Rostami et al 2019). In New Zealand, the small amount of seroprevalence data is summarised in Figure 2. Parasites appear to have patience and will often arrest their development in order to wait for a time of immunocompromise within the host. Young growing animals and animals under stress from disease or malnutrition and pregnancy or lactation are at particular risk. It is no surprise then to see higher seropositivity in specific populations screened by the 1988 by Christchurch School of Medicine, such as post-partum women as a relaxation in immune response allows recrudescence (Williamson et al 1988). The 83% of rural Māori children testing positive on the East Coast should surely be readdressed, knowing what we now know about the detrimental effects of *Toxocara* seropositivity in children.

The veterinary perspective

Veterinarians almost universally recommend regular deworming of puppies and kittens, as we know that prevalence and morbidity is high in this age group. As animals get into adulthood, prevalence (based on eggs seen in faeces) usually falls below 5% (Rostami et al 2020). *Toxocara* in adult animals is generally non-pathogenic, and so veterinarians do not commonly place a high level of importance around deworming. Testing (by coproscopy) and treating is not an economically viable option for owners, and so we are left with the option of advising regular deworming of all animals in order to eliminate shedding as much as possible. The recommendation from most veterinarians for decades now is to deworm four times a year. However, many de-wormers are only effective against adult worms, and as the prepatent period of *Toxocara* is just over a month, significant egg shedding into the environment can still occur. Owner compliance with these recommendations is, however, low (Pennelegion et al 2020). One progressive national veterinary practice has reviewed the recent public health concerns and are now recommending monthly worming of pets to clients with young children under five or immunocompromised individuals in the house.

There is concern from the profession around 'overmedication' and the possibility of resistance development. Although there are no reports worldwide of resistance to anthelmintics in *Toxocara* spp. (ESCCAP, 2020), this perceived risk outweighs the public health risk for the majority of veterinarians currently, given the lack of data from a New Zealand public health perspective.

Environmental contamination control

Removing faeces from the environment would make the greatest gains in the protection of the public. Unfortunately, the feline population, both owned and stray/feral, contribute to environmental contamination and removal of their faeces is an impractical solution. Somewhat luckily, the impact of cats on native birds led to the formation of The National Cat Management Strategy Group in 2014 by eight national organisations. The group's aim is to develop a national overarching strategy for responsible, caring and humane cat management in New Zealand. Without intention, this initiative could have a large positive impact on public health as a recent study showed that 78% of stray/feral cats in New Zealand were shedding *Toxocara* eggs (Scott 2020). With an estimated 200,000 stray/feral cats in New Zealand, there's a lot of environmental contamination to be controlled. Other sensible recommendations are to protect sandpits from cat faeces, educate on the importance of good hand hygiene, particularly after gardening, washing vegetables well and cooking meat and offal adequately.

Public health

This is a call to any medical professionals who think that this zoonotic disease warrants further investigation in New Zealand. I am unaware of any research work currently underway here, but I am keen to hear from you with information that I may have missed or ideas for future collaboration in line with the One Health philosophy.

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