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REVIEW

NEUROTOXOCAROSIS

Josef FINSTERER(1) & Herbert AUER(2)

SUMMARY

Infection of humans with embryonated eggs of *Toxocara canis* (larva migrans) remains asymptomatic, or results in covert or common toxocarosis, visceral larva migrans syndrome, or ophthalmologic and neurologic impairment. Though neurological manifestations of *Toxocara canis* larvae are rare, toxocarosis remains an important differential diagnosis of various neurological disorders. Manifestations of the central nervous system are dementia, meningo-encephalitis, myelitis, cerebral vasculitis, epilepsy, or optic neuritis. Manifestations of the peripheral nervous system comprise radiculitis, affection of cranial nerves, or musculoskeletal involvement. If toxocarosis is neglected, ignored, or refused as a differential of these abnormalities, it may be easily overlooked for years. Early recognition and treatment of the infection is, however, of paramount importance since it reduces morbidity and mortality and the risk of secondary superinfection. Like the visceral manifestations, neurological manifestations of toxocarosis are treated by benzimidazole components, most frequently albendazole, corticosteroids, or diethylcarbamazine. If detected and treated early, the prognosis of neurological manifestations of toxocarosis is favourable.

KEYWORDS: Toxocarosis; Parasitosis; Nervous system; Infection; Larva migrans syndrome; Helminthosis; Albendazole.

INTRODUCTION

Despite increased knowledge about hygiene worldwide and availability of potent anti-helminthic drugs, the prevalence of helminthoses is still high. This is because of inappropriate application of hygienic measures and because of the globalization and mobility, which allows worldwide distribution of parasites also to the Western world. One of the most frequently occurring helminthosis is the infection with the larvae of the nematodes *Toxocara canis* and *Toxocara cati* respectively [KAYES, 1997; MAGNAVAL *et al.*, 2001]. Though these parasites rarely affect the central or peripheral nervous system (CNS, PNS), toxocarosis remains a differential diagnosis of various neurological disorders. The following review gives an overview on the current knowledge about the neurological implications of toxocarosis, which are frequently overlooked if toxocarosis is neglected, ignored, or refused as a differential. Early recognition and treatment of the infection is of paramount importance since it reduces morbidity and mortality and the risk of secondary superinfection [MAGNAVAL *et al.*, 2001].

HISTORY

Human infection with *Toxocara canis* has been first described in the late fourties and early fifties. First evidence for CNS toxocarosis has been given by BEAUTYMAN & WOOLF in 1951. On autopsy they found a larva in the left thalamus of a child, whose death was attributed to poliomyelitis [BEAUTYMAN & WOOLF, 1951]. In 1952 the term "visceral larva migrans syndrome" (VLM) was coined for children with eosinophilia and long-term multi-system disease [BEAVER *et al.*, 1952]. Further evidence for CNS toxocarosis came from a case report by DENT *et al.* in 1956. Also in 1956 the causative organism of toxocarosis was detected [TAYLOR, 2001] and NICHOLS *et al.,* 1956 provided more data on the morphology of the worm and its eggs and larvae. Since then several case studies and case reports and a high number of animal studies has augmented the knowledge about all aspects of toxocarosis, particularly about neurotoxocarosis. The term covert toxocarosis was coined and defined by BASS *et al.* and TAYLOR *et al.* in 1987. About 50 patients with CNS or PNS toxocarosis have been reported so far.

INFECTIOUS AGENT AND WAY OF TRANSMISSION

Toxocarosis is caused by ingestion of the eggs of *Toxocara canis*, a roundworm in dogs, puppies, and cats [GARCIA-PEDRIQUE, 2004; PREISS, 1982]. The Toxocara roundworm is a nematode of the Ascaridae family which normally parasites the small intestine of its hosts [GLICKMAN & SCHANTZ, 1981; MAGNAVAL *et al.,* 2001; PECINALI *et al.,* 2005]. Female worms produce up to 200000 eggs/d,

(1) Neurological Department, Krankenanstalt Rudolfstiftung.
(2) Department of Medical Parasitology, Institute of Hygiene and Medical Microbiology, Medical University of Vienna, Vienna, Austria.
Correspondence to: Univ. Prof. DDr. J. Finsterer, Postfach 20, 1180 Vienna, Austria. Tel. +43-1-71165-92085. Fax. +43-1-4781711. E-mail: fifigs1@yahoo.de

which pass to the feces, are not infective, and require an incubation period in the soil to embryonate [GLICKMAN & SCHANTZ, 1981]. Humans are accidentally infected by direct contact with dogs [WOLFE & WRIGHT, 2003], ingestion of embryonated eggs from soil (geophagia, pica), or after exposure to dirty hands (poor hygiene), raw vegetables, or to larvae from undercooked giblets [NAGAKURA *et al.,* 1989; SALEM & SCHANTZ, 1992; XINOU *et al.,* 2003]. After ingestion embryonated eggs hatch in the intestines, larvae penetrate the intestinal wall, and then migrate via the blood circulation to the liver, lungs, and left heart, from where they disseminate via the systemic circulation to eyes, brain, and muscle [DUNSMORE *et al.,* 1983; KAPLAN *et al.*, 2004; MAGNAVAL *et al.*, 2001]. Larvae do not grow at these sites but become encapsulated by a collagenous reaction, manifesting as eosinophilic granuloma, and are metabolically active [XINOU *et al.,* 2003]. They secrete an array of enzymes, waste products, and cuticular components, which cause tissue damage, necrosis, and a marked inflammatory reaction, with eosinophils as the major component [XINOU *et al.,* 2003]. There are indications that toxic proteins from these eosinophils are released and contribute to the pathology and symptomatology of toxocarosis [KAYES, 1997].

The migratory pathway of *Toxocara canis* larvae after oral ingestion or artificial inoculation has been extensively studied in various animals. According to these studies *Toxocara canis* embryonated eggs reach the liver of NIH mice two days after infection and the lung three days after oral infection [ABO-SHEHADA & HERBERT, 1984]. Also the kidneys may be affected early. Larvae are then dispersed throughout the body and enter the myotropic/neurotropic phase (affection of the CNS or musculature) by day seven [ABO-SHEHADA & HERBERT, 1984; PECINALI *et al.,* 2005]. If larvae are experimentally injected into the brain they are also capable of migrating from the brain to the viscera and musculature. Considerable pathology occurs due to larval migration and acute and chronic disease is recorded [ABO-SHEHADA & HERBERT, 1984]. There is a significant relation between the duration of infection, inoculum size, and dispersal rate of the larvae [EL-SHAZLY *et al.,* 1991].

EPIDEMIOLOGY

As many as one billion humans are infected with animal parasites [DONOVICK AND BURRIGHT, 1987]. One of the most prevalent is *Toxocara canis* [MAGNAVAL *et al.,* 2001]. The seroprevalence is particularly high in developing countries, especially in rural areas, and also some tropical islands [XINOU *et al.,* 2003]. Human toxocarosis is predominantly frequent in areas where the stray and *Toxocara canis* infected dog population is big [KAPLAN *et al.,* 2004]. The prevalence of *Toxocara canis* infections in dogs is variable and amounts to 4.3% in Japan [ITOH *et al.,* 2004], 17% in Austria, or 66% in the USA [DONOVICK & BURRIGHT, 1987]. Particularly, in many rural areas worldwide infection rates may be even higher. Additionally, 40% of the foxes and up to 67% of the cats are infected in Austria [AUER & ASPÖCK, 1998]. An area is considered to pose a high risk for *Toxocara canis* infection when the infection rate among dogs is > 7% [XINOU *et al.,* 2003]. There is a strong correlation between the infectious risk, life style and *Toxocara* sero-prevalence. Children are more frequently affected than adults [GARCIA-PEDRIQUE *et al.,* 2004]. On the average, 7% of all humans carry antibodies against *Toxocara canis* [DONOVICK AND BURRIGHT, 1987], but there is a broad range depending on the tested location [DE ANDRADE LIMA COELHO *et al.,* 2005; GARCIA-PEDRIQUE *et al.,* 2004; AGUIAR-SANTOS *et al.,* 2004]. From Reunion a seroprevalence of 93% in adults and from Saint-Lucia a seroprevalence of 86% in children has been reported [THOMPSON *et al*., 1986]. In a study on mountain aboriginal schoolchildren in Taiwan the overall seroprevalence of toxocarosis was 77% [FAN *et al.,* 2004]. In Bali a seroprevalence of 63% has been found [MAGNAVAL *et al.,* 1994]. In a study on 386 Brazilian children the frequency of IgG antibodies against *Toxocara* was 39% [AGUIAR-SANTOS *et al.,* 2004]. Intestinal helminths were present in 52% of individuals that underwent coprological examination [AGUIAR-SANTOS *et al.,* 2004]. In another Brazilian study the frequency of positive serology for toxocara was 30% [MOREIRA-SILVA *et al.,* 2004]. In a study on 150 Lebanese subjects the seroprevalence was 19% [KANAFANI *et al.*, 2006]. The annual incidence rate in a study on 75 individuals from the São Paulo area was 18% [ANARUMA FILHO *et al.*, 2003].

VISCERAL MANIFESTATIONS

Humans who ingest *Toxocara canis* eggs may remain unaffected or may manifest a mono- or multi-system disease with symptoms arising from larval invasion of different organs [BACHLI *et al.*, 2004; RUTTINGER & HADIDI, 1991]. The degree of host damage is dependent on the tissue affected, the number of migrating juveniles, the level of immunocompetence, and the host's age [DESPOMMIER, 2003]. Additionally, pathological consequences are dependent on the death of the juveniles [DESPOMMIER, 2003]. Death of larvae induces immediate-type and delayed-type hypersensitivity responses. Immediate-type hypersensitivity responses manifest clinically as classical VLM [DESPOMMIER, 2003]. The organs most frequently affected are the liver, lungs, eyes, CNS, myocardium, or musculature [HARALAMBIDOU *et al.*, 2005; RUTTINGER & HADIDI, 1991]. Accordingly, toxocarosis can be classified as: 1. Classical or incomplete VLM. 2. Neurological toxocarosis, including ocular involvement (ocular larva migrans syndrome). 3. Covert or common toxocarosis [TAYLOR *et al.,* 1987]. 4. Asymptomatic toxocarosis [AUER & ASPÖCK, 2004; BASS *et al.,* 1987; HAYASHI *et al.,* 2003; TAYLOR *et al.,* 1987; TRABELSI *et al.,* 2004]. In the majority of the cases, *Toxocara canis* infection remains clinically unapparent. Covert toxocarosis is present when in patients with only mild, focal impairment without systemic manifestations, toxocarosis remains unrecognized [AUER & ASPÖCK, 2004; KAWAJIRI *et al.,* 2001]. Overt toxocarosis usually manifests in children as fever, anorexia, vomiting, lethargy, sleep and behavior disorders, pharyngitis, pneumonia, cough, wheeze, limb pain, cervical lymphadenitis, or hepatomegaly [MAGNAVAL *et al.,* 2001]. Common toxocarosis is only loosely related to a clinical form but is most frequently associated with weakness, pruritus, rash, impaired breathing, and abdominal pain [MAGNAVAL *et al.,* 2001]. VLM is usually seen in preschool children [PREISS, 1982] and characterized by general illness with fever, skin rash, abdominal symptoms due to hepatomegaly or splenomegaly, respiratory symptoms (particularly bronchospasm) due to pulmonary infiltrations, myalgias, arthralgias, anorexia, persistent eosinophilia of more than 30%, leucocytosis, and hyper-gammaglobulinemia [BARRA *et al.,* 1996; OTA *et al.,* 1994; PREISS, 1982; PECINALI *et al.,* 2005; XINOU *et al.,* 2003]. In the liver of patients with VLM granulomatous lesions can be found [HILL *et al.,* 1985; LEONE *et al.,* 2005]. In rare cases toxocarosis may manifest as colicky abdominal pain and ascites [CHIRA *et al.,* 2005]. VLM usually results

in a benign self-limited course [MOREIRA-SILVA *et al.,* 2004]. Toxocarosis has been also associated with allergy-related syndromes, like chronic urticaria, reactive arthritis, or angioedema [ISMAIL & KHALAFALLAH, 2005; MAGNAVAL *et al.,* 2001].

NEUROLOGICAL MANIFESTATIONS

A) CNS involvement: CNS involvement due to *Toxocara* sp. has been documented only in about 50 patients [BACHLI *et al.,* 2004; BOUCHARD *et al.,* 1998; GOFFETTE *et al.,* 2000; HUISMANS, 1980; MOREIRA-SILVA *et al.,* 2004; OSOEGAWA, 2004] although in experimental animals larva migrans frequently migrates to the brain [FAN *et al.,* 2003; GOOD *et al.,* 2001; COX & HOLLAND, 1998]. The exact frequency of CNS involvement in toxocarosis is unknown and varies with different species of migrating larvae [MOREIRA-SILVA *et al.,* 2004]. In a study on 308 autopsies of children the frequency of CNS granulomas due to larva migrans was 0.68%. In another study epilepsy was found in 5% of the patients with VLM [LEWIS *et al.,* 1962]. Other studies however, showed that toxocara infection is frequently not associated with obvious neurological abnormalities although antibodies against *Toxocara canis* were repeatedly found in the CSF of these patients [MOREIRA-SILVA *et al.,* 2004].

The site of the CNS invasion depends on multiple factors, like number of ingested larvae, genetic factors of the host, and whether previous exposure had occurred [XINOU *et al.,* 2003]. CNS involvement comprises meningitis [ENGEL *et al.,* 1971; MOREIRA-SILVA *et al.,* 2004; OSOEGAWA, 2004], encephalitis [MOREIRA-SILVA *et al.,* 2004; OTA *et al.,* 1994], myelitis [ENGEL *et al.,* 1971; GOFFETTE *et al.,* 2000; KAWAJIRI *et al.,* 2001; OSOEGAWA, 2004; OTA *et al.,* 1994; SELLAL *et al.,* 1992; YOSHIDA *et al.,* 2004], cerebral vasculitis [DOUSSET *et al.,* 2003], or optic neuritis [HAYASHI *et al.,* 2003; KOMIYAMA *et al.,* 1995] (Table 1). CNS toxocarosis is related to the number of larvae entering the brain and to the severity of CNS damage and inflammation [XINOU *et al.,* 2003]. Following these manifestations, affected patients complain about headache, fever, oversensitivity to light, weakness, dorsalgia, confusion, tiredness, and visual impairment. In mice behavioral changes have been reported and were related to the number of larvae accumulated in the brain [COX & HOLLAND, 1998; HAMILTON *et al.,* 2006; SKERRETT & HOLLAND, 1997]. Despite the identification of the risk factors rural residence, ownership of dogs, and dementia for CNS toxocarosis by a multivariate logistic regression analysis, a recognizable neurologic defect has not been identified [MAGNAVAL *et al.,* 1997]. Most of the cases with CNS toxocarosis on autopsy did not present with clinical CNS manifestations [MOREIRA-SILVA *et al.,* 2004]. CNS toxocarosis may occur at all ages and it appears that there is no gender preponderance [MOREIRA-SILVA *et al.,* 2004]. There may be eosinophilia exclusively in the CSF and vice versa focal CNS lesions with blood eosinophilia but normal CSF findings [VIDAL *et al.,* 2003], why a negative spinal tap does not rule out CNS toxocarosis. In animals CNS toxocarosis manifested as cerebellar ataxia [AKAO *et al.,* 2003].

1. Dementia: Dementia and depression have been reported only in a single patient as a manifestation of CNS toxocarosis [RICHARTZ & BUCHKREMER, 2002]. In a 65-year-old woman with a long-lasting history of depression and cognitive decline CSF investigations revealed eosinophilia and antibodies against *Toxocara canis* antigen. Treatment with albendazole improved the cognitive deficits. The infection was assumed to have occurred years before when the woman was working as a shepherd in close contact with dogs [RICHARTZ & BUCHKREMER, 2002]. Even if the infection had occurred already years before the clinical manifestations, affected patients may profit from specific anti-helminthic therapy [RICHARTZ & BUCHKREMER, 2002]. CNS toxocarosis may also manifest as behavioral disturbances [CRITCHLEY *et al.,* 1982]. In a study on 155 children seropositivity to *Toxocara* was associated with adverse neuropsychological effects [MARMOR *et al.,* 1987]. In a study on 77 children seropositivity was associated with poor reading achievement, marked distractibility, and lower intelligence [WORLEY *et al.,* 1984].

2. Eosinophilic meningo-encephalitis: Eosinophilic encephalitis is a rare manifestation of a *Toxocara canis* infestation and has been reported in single patients [BARRA *et al.,* 1996; GOULD *et al.,* 1985; MIKHAEL *et al.,* 1974; MIMOSO *et al.,* 1993; MRISSA *et al.,* 2005; SOMMER *et al.,* 1994; VILLANO *et al.,* 1992]. In a 21-year-old woman eosinophilic meningo-encephalitis manifested as frontal headache, fever, ataxia, meningeal irritation, epilepsy, and pleocytosis [OTA *et al.,* 1994]. She had been in close contact with a dog. Cerebral MRI showed several T2-hyperintense cortical and subcortical lesions, which enhanced with gadolinium [OTA *et al.,* 1994]. Antibodies against the *Toxocara canis* antigen were positive in the serum and CSF. Under a therapy with diethyl-carbamazine and corticosteroids the manifestations resolved [OTA *et al.,* 1994]. In a 2-year-old boy with headache,

Table 1
Neurological manifestations of toxocarosis

Central nervous system	**Reference**
Cerebral vasculitis	DOUSSET *et al*., 2003; OUJAMAA *et al.*, 2003
Eosinophilic meningitis	GOFETTE, 2000; MOREIRA-SILVA *et al*., 2004; OTA *et al*., 1994; VIDAL *et al.*, 2003
Eosinophilic encephalitis	MOREIRA-SILVA *et al.*, 2004; VIDAL *et al.*, 2003
Eosinophilic myelitis	GOFETTE *et al.*, 2000; MOREIRA-SILVA *et al.*, 2004; OLSON & PETTEWAY, 1972
Epilepsy	BACHLI *et al.*, 2004; ARPINO *et al.*, 1990; NICOLETTI *et al.*, 2002
Optic neuritis	HAYASHI *et al.*, 2003; KOMIYAMA *et al*., 1995
Peripheral nervous system	
Radiculitis	MOREIRA-SILVA *et al.*, 2004
Skeletal muscle affection	SUGANE & OSHIMA, 1982
7th cranial nerve affection	personal communication

confusion, weakness, clinical neurologic examination revealed lethargy, irritability, nuchal rigidity, weakness and accentuated deep tendon reflexes, extensive diagnostic work-up disclosed eosinophilic pleocytosis, and antibody testing revealed a *Toxocara canis* infection [VIDAL *et al.,* 2003]. In a 54-year-old female encephalitis manifested on cerebral MRI as several enhancing subcortical white matter lesions in both lobes [XINOU *et al.,* 2003]. A 48-year-old patient with *Toxocara canis* encephalitis presented with ataxia, rigor, and neuropsychological disturbances [SOMMER *et al.,* 1994]. Imaging studies revealed diffuse, circumscribed white matter lesions and occlusion of various branches of the middle cerebral artery [SOMMER *et al.,* 1994]. Antihelminthic therapy was only initially effective and, because of progression, had to be enhanced by corticosteroids and azathioprine [SOMMER *et al.,* 1994]. Cerebral lesions of toxocarosis locate predominantly in the cerebral and cerebellar white matter with or without the presence of larvae [KAYES & OAKS, 1978]. The presence or absence of larvae within these lesions is due to the fact that larvae are not permanently trapped by the host reaction but can escape from the reaction, migrate elsewhere and elicit the same reaction anew [XINOU *et al.,* 2003]. This is why the cellular composition of granulomas does not indicate the length of the infection [KAYES & OAKS, 1978].

3. Myelitis: Affection of the myelon by the larvae has been repeatedly reported [DAURIAC-LE MASSON *et al.,* 2005; GOFETTE *et al.,* 2000], usually in association with encephalitis or meningitis [EBERHARDT *et al.,* 2005; ENGEL *et al.,* 1971] but also isolated [SELLAL *et al.,* 1992]. In a 40-year-old woman, eosinophilic myelitis resulted in subacute weakness of the right leg and dysesthesias in the dermatomas Th8-10. MRI studies of the myelon revealed an abnormal hyperintensity within the spinal cord and CSF investigations revealed eosinophilic pleocytosis [GOFETTE *et al.,* 2000]. The neurological abnormalities resolved completely after mebendazole therapy [GOFETTE *et al.,* 2000]. In a young woman recurrent myelitis was attributed to larva migrans infection after detection of eosinophilia in the serum and CSF, antibodies against *Toxocara* and a favorable response to diethylcarbamazine (DEC) [SELLAL *et al.,* 1992]. Meningo-myelitis was also reported by others [DAURIAC-LE MASSON *et al.,* 2005; ENGEL *et al.,* 1971; SELLAL *et al.,* 1992]. In these reports spinal MRI showed solitary or multiple, strongly and homogeneously enhancing T2-hyperintense lesions [DUPREZ *et al.,* 1996; GOFETTE *et al.,* 2000; KUMAR & KIMM, 1994; STRUPP *et al.,* 1999]. In most of these cases the CNS was the organ exclusively affected by the infection [XINOU *et al.,* 2003]. Some Japanese cases presented with sensory disturbances (positive Lhermitte sign, paresthesias, hyperesthesia), extensive, enhancing spinal cord lesions on T2-weighted MR images, and mild CSF eosinophilia [OSOEGAWA, 2004]. In a 27-year-old woman *Toxocara canis* myelitis manifested as back pain, positive Lhermitte sign, mild blood eosinophilia, mildly increased IgE levels, and CSF eosinophilia. In a single case toxocarosis manifested as spinal dural abscess [RUSSEGGER & SCHMUTZHARD, 1987].

4. Cerebral vasculitis: Only single angiographically documented cases with cerebral vasculitis have been reported [DOUSSET *et al.,* 2003; HAMIDOU *et al.,* 2002; OUJAMAA *et al.,* 2003; SOMMER *et al.,* 1994]. In one of these cases occlusion of multiple small branches of the middle cerebral artery with multiple consecutive brain infarcts has been found. Cerebral infarction close to the cerebral granulomas was also detected in another case [XINOU *et al.,* 2003]. Cerebral vasculitis may even develop during antihelminthic treatment. Whether infarctions in these cases were due to the acute inflammatory reaction against the antigen or due to a delayed-type hypersensitivity to antihelminthic therapy remains questionable [XINOU *et al.,* 2003].

5. Epilepsy: There are several reports showing an association between a positive *Toxocara canis* serology and seizures [ARPINO *et al.,* 1990; NICOLETTI *et al.,* 2002; OTA *et al.,* 1994]. There are estimations according to which 12000-15000 of epilepsy cases in Britain are attributable to CNS toxocarosis [PIEKARSKI, 1987]. In another study epilepsy was found in three of 58 patients with VLM [LEWIS *et al.,* 1962]. Seizures have been reported as the initial CNS manifestation of toxocarosis in quite a number of patients [BACHLI *et al.,* 2004]. In an 11-year-old girl with generalized epileptic seizures due to a focal cerebral mass lesion and blood eosinophilia, toxocarosis was diagnosed after resection of the lesion [BACHLI *et al.,* 2004]. After albendazole the patient recovered completely without sequelae.

6. Optic neuropathy: Ocular abnormalities are a frequent complication of toxocarosis. Ocular *Toxocara canis* infection usually manifests as visual loss from optic neuritis when there is simultaneous cerebral toxocarosis [KOMIYAMA *et al.,* 1995]. Uveitis, or chorio-retinitis may also occur [MACARIE *et al.,* 2005; STEWART *et al.,* 2005]. *Toxocara canis* uveitis usually manifests unilaterally and may present as peripheral granuloma of the retina, papillitis, macular granuloma, or as vitreous inflammation, mimicking endophthalmitis [STEWART *et al.,* 2005]. Secondary glaucoma can follow [DESPOMMIER, 2003]. In a study on 68 patients with posterior pole granuloma antibodies against *Toxocara* were detected in 17% of them [MIRDHA & KHOKAR, 2002]. According to findings in Mongolian gerbils, a useful animal model for toxocarosis, larvae migrate from the cerebrum to the eye through the optic nerve arriving there by day nine after inoculation [HAYASHI *et al.,* 2003]. Other studies demonstrated ocular affection by the infection already three days after oral infection [HAYASHI *et al.,* 2003]. According to these data there are two migration pathways to the retina in ocular toxocarosis, an early hematogenic pathway and a late pathway along the optic nerve [HAYASHI *et al.,* 2003].

B) Peripheral nervous system involvement: PNS manifestations of toxocarosis are rare and comprise radiculitis, affection of cranial nerves, or musculo-skeletal involvement. However, PNS manifestations are presumably more frequent than previously reported.

1. Radiculitis: Radiculitis is a rare manifestation of neurotoxocariasis and usually occurs together with meningitis [ROBINSON *et al.,* 2002]. The diagnosis is based on the clinical findings (reduced tendon reflexes, muscle weakness, muscle wasting fasciculations), CSF findings (eosinophilia, positive antibodies against *Toxocara canis* antigen), and abnormal nerve conduction studies (abnormal F-wave studies, proximal neuropathy), or electromyography (neurogenic electromyogram).

2. Cranial nerves other than the optic nerve: Larva migrans of *Toxocara canis* involving cranial nerves almost exclusively concerns the optic nerve [HAYASHI *et al.,* 2003]. Larva migrans of *Toxocara canis* associated with affection of other cranial nerves has not been reported but peripheral facial palsy with atypical facial pain and swollen

cervical lymph nodes may be a rare PNS manifestation of toxocarosis [personal communication]. In a patient with a peripheral seventh cranial nerve palsy diagnostic work-up revealed antibodies against *Toxocara canis* in the CSF. This patient profited shortly from a therapy with albendazole. That he did not develop neurological abnormalities other than the cranial nerve palsy is surprising, but may be attributed to the generally mild CNS manifestations of neurotoxocarosis. Obviously, more patients than assumed carry larvae but do not develop clinical neurological manifestations of the disease. Arguments for CNS toxocarosis in this case were the presence of *Toxocara canis* antibodies in the CSF, and bilaterally enlarged cervical lymph nodes. Transmigration of serum *Toxocara canis* antibodies via the blood brain barrier into the CSF is rather unlikely given the absence of any reports confirming such a scenario. On the other hand absence of pleocytosis and eosinophilia in the CSF does not exclude CNS toxocarosis, particularly after three previous albendazole cycles and the presumably long interval between the acute infection and antibody determination. Also repeatedly normal imaging studies of the brain do not exclude CNS toxocarosis. Assuming CNS toxocarosis as the cause of a Bell's palsy, either the infundibular (intracerebral) portion of the nerve must have been affected from focal encephalitis, meningitis, or radiculitis, or the larvae infiltrated the nerve and migrated centrifugally.

3. Skeletal muscle involvement: Migration of larva migrans to the musculature has been only rarely reported in humans [RAYES & LAMBERTUCCI, 1999; RAYES *et al.,* 2000; SUGANE & OSHIMA, 1982]. Usually, muscular toxocarosis manifests as pyomyositis, accompanied by the development of muscular abscesses, granuloma formation around larvae, and tissue necrosis [RAYES & LAMBERTUCCI, 1999; SUGANE & OSHIMA, 1982]. In single cases muscular affection may also manifest as focal myositis, resulting in unilateral swelling of a leg [WALSH *et al.,* 1988] or as severe necrotic pyomyositis, requiring urgent surgical debridement [LAMBERTUCCI *et al.,* 1998]. In mice however, affection of the skeletal muscles by the infection is a frequent finding [FAN *et al.,* 2003].

Diagnosis: Diagnosis of CNS and PNS involvement of toxocarosis is based on the history, the clinical neurologic investigation, blood tests, including differential blood cell count, and CSF investigations, including determination of antibodies against *Toxocara canis* antigen in the CSF, and imaging methods, including cerebral CT scans, cerebral MRI, and cerebral angiography. PNS involvement can be recognized when applying nerve conduction studies, F-wave studies, electromyography, CSF investigations, or muscle/nerve biopsy. Granuloma formation around larvae within the skeletal muscle can also be detected by imaging methods like ultrasound, CT, or MRI of the muscle [SUGANE & OSHIMA, 1982]. Since the prevalence of toxocarosis is high in patients with unknown eosinophilia, these patients should undergo antibody testing [KWON *et al.,* 2006]. Generally, the diagnosis of neurotoxocarosis requires the following findings: 1. High titres of *Toxocara canis* antibodies in the serum. 2. High titers of *Toxocara canis* antibodies in the CSF. 3. Eosinophilia in the serum or CSF. 4. Clinical and radiologic improvement and normalization of CSF abnormalities upon anti-helminthic therapy [XINOU *et al.,* 2003].

1. Blood chemical investigations: Eosinophilia can be almost always found in VLM, but may be absent in single patients with covert or common toxocarosis [MAGNAVAL *et al.,* 2001]. On the contrary, in ocular or CNS toxocarosis eosinophilia is frequently absent [MAGNAVAL *et al.,* 2001]. Another promising diagnostic parameter is elevated serum IgE [MAGNAVAL *et al.,* 2001]. The most commonly used diagnostic test is the ELISA with TES-antigen. A positive ELISA can be confirmed by Western blot [MAGNAVAL *et al.,* 2001], which is as sensitive as the ELISA and quite specific [MAGNAVAL *et al.,* 2001]. Concerning the interpretation of the serological results, individuals with positive antibodies but absent clinical manifestations rather represent past than present infection [MAGNAVAL *et al.,* 2001]. Seropositivity associated with eosinophilia, however, indicates active toxocarosis. In patients with covert or common toxocarosis but absent eosinophilia, increase in IgE provides evidence for active toxocarosis [MAGNAVAL *et al.,* 2001]. Care must be taken concerning the reliability of *Toxocara canis* antibody titers in the serum and even CSF, since they are often normal or borderline, particularly in patients with sole CNS manifestations [XINOU *et al.,* 2003].

2. Radiological investigations: Cerebral MR images show cortical or sub-cortical, multifocal, circumscribed, homogeneously enhancing T2-hyperintense lesions or a combination of circumscribed and diffuse changes [KOMIYAMA *et al.,* 1995; RUTTINGER & HADIDI, 1991; SOMMER *et al.,* 1994; ZACHARIAH *et al.,* 1994]. These lesions are hypodense on cerebral CT and hypointense on T1-weighted MR images. Along with the CNS inflammation, areas of hemorrhage can be detected [XINOU *et al.,* 2003]. Occasionally, there is focal meningeal enhancement suggesting extension of the inflammation to the subarachnoidal space [XINOU *et al.,* 2003]. T1- and T2-hyperintense cortical areas are interpreted as cortical necrosis, presumably due to multiple brain infarcts caused by immune vasculitis [XINOU *et al.,* 2003]. Generally, cerebral CT and MRI findings in neurotoxocarosis are non-specific and for establishing the diagnosis the above mentioned criteria need to be fulfilled. Serial MR imaging studies, however, are a valuable tool to monitor the disease course. In case of myelitis spinal MRI may show enhancing T2-hyperintensities [OSOEGAWA, 2004].

Differential diagnoses: Toxocarosis is not the only helminthic infection, which causes eosinophilic meningo-encephalitis. Eosinophilic meningo-encephalitis may also occur together with infections from Baylisascaris procyonis, Gnathostoma spinigerum, *Angiostrongylus cantonensis, Coccidioides immitis*, or together with cysticercosis, ascaridiosis, trichinosis, strongyloidosis, echinococcosis, schistosomiosis, paragonimiosis, or fascioliosis [VIDAL *et al.,* 2003]. Transient CSF eosinophilia can be also observed in tuberculosis, syphilis, or lymphoma involving the meninges [VIDAL *et al.,* 2003].

Therapy: There is a general lack of well-controlled studies on the therapy of neurotoxocarosis, being attributed to the rarity of the disease. Amongst all available drugs albendazole is the most commonly used and the treatment of choice [PAWLOWSKI, 2001]. However, other benzimidazole components, like oxibendazole, flubendazole, or thiabendazole [FOK & KASSAI, 1998; LEONE *et al.,* 2005] have a similar effect [PAWLOWSKI, 2001]. Positive experiences also exist with DEC [REY *et al.,* 2005]. Concerning the efficacy of ivermectin, it cannot be recommended for human toxocarosis at the moment [MAGNAVAL *et al.,* 2001]. The blood-brain barrier is principally permeable for all available antihelminthic drugs [FOK & KASSAI, 1998], but benzimidazoles other than albendazole are poorly absorbed outside the gastrointestinal tract. Administration of albendazole three times per day

is more effective than a single daily dose [DELGADO *et al.,* 1989]. Albendazole gives better results than other antihelminthic drugs, because it reaches higher serum concentrations, has a better penetration into the CSF, and is less toxic [VIDAL *et al.,* 2003]. Neurotoxocarosis may also resolve from thiabendazole [RUSSEGGER & SCHMUTZHARD, 1987] or DEC [RUTTINGER & HADIDI, 1991] alone, or from a combination of corticosteroids with DEC [KOMIYAMA *et al.,* 1995], corticosteroids and mebendazole [DUPREZ *et al.,* 1996], or corticosteroids and thiabendazole [KUMAR & KIMM, 1994].

In case of ocular involvement the additional administration of corticosteroids is recommended [RICHARTZ & BUCHKREMER, 2002]. Particularly, the *Toxocara canis* optic neuropathy is sensitive to corticosteroids [COX *et al.,* 1993]. Except for ophthalmologic toxocarosis there is no consensus concerning the utility of corticosteroids for CNS toxocarosis [VIDAL *et al.,* 2003]. Corticosteroids administered during *Toxocara canis* infestation may even result in a significant increase in brain parasitism and total larval count [MOHAMED *et al.,* 1994]. If *Toxocara canis* endophthalmitis is non-responsive to the common surgical and medical approach (vitrectomy, antihelminthics, corticosteroids) cyclosporine A may be helpful [BARISANI-ASENBAUER *et al.,* 2001; MORA *et al.,* 2005; LESCANO *et al.,* 2004].

Administration of specific antihelminthic drugs for CNS toxocarosis usually resolves the clinical neurologic impairment, but morphological lesions, found on imaging studies, only rarely decrease in size or number [RUTTINGER AND HADIDI, 1991]. Several experimental approaches resulted in promising results, like the glucan immunemodulator combined with immunoglobulin and zinc [SOLTYS *et al.,* 1996]. In addition to the pharmacological treatment, CNS toxocarosis requires thorough prevention of recontamination by deworming dogs and sanitary education [MAGNAVAL *et al.,* 2001].

CONCLUSIONS

Toxocara canis infestation is a worldwide problem and manifests as VLM, ocular larva migrans syndrome, covert toxocarosis or common toxocarosis or remains asymptomatic. Rarely, CNS and PNS are involved, manifesting as encephalopathy with cognitive decline, meningo-encephalitis, cerebral vasculitis, epilepsy, visual impairment, myelitis, radiculitis, cranial nerve involvement, or skeletal muscle affection. Transmission from animal to human is favored by the cohabitation with dogs and cats, poor hygiene, and by frequenting public parks and playgrounds. Prophylactic measures aim to limit access to contaminated soil, to regularly deworm pets, to reduce the number of domestic animals, and to limit their access to areas frequented by young children. Future control programs require cheap and effective diagnostic approaches, the development of vaccines, which offer lifelong protection, and effective and safe single-dose treatments. If detected and treated early, the prognosis of neurological manifestations of toxocarosis is favorable. Monitoring of CNS involvement in toxocarosis is best carried out by repeated MRI investigations. Serial serum tests for *Toxocara* antibodies are not useful for monitoring the disease course, since they may remain positive for months or years, even after clinical recovery. Blood eosinophilia should be thoroughly examined for helminthosis. CSF eosinophilia is no prerequisite for CNS toxocarosis.

RESUMO

Neurotoxocaríase

Infecção humana com ovos embrionados de *Toxocara canis* (larva migrans) pode permanecer assintomática ou resultar em toxocaríase acentuada ou comum, síndrome da larva migrans visceral ou manifestações neurológicas ou oftalmológicas. Embora manifestações neurológicas das larvas de *Toxocara canis* sejam raras, a toxocaríase permanece como importante diagnóstico diferencial de várias manifestações neurológicas. Manifestações do sistema nervoso central são demência, meningoencefalite, mielite, vasculite cerebral, epilepsia, ou neurite ótica. Manifestações do sistema nervoso periférico compreendem radiculite, agressão de nervos cranianos ou envolvimento músculo-esquelético. Se a toxocaríase é negligenciada, ignorada, ou recusada como diferencial destas anormalidades, ela pode ser facilmente desapercebida por anos. Reconhecimento precoce de tratamento da infecção é portanto de fundamental importância uma vez que reduz sua morbidade e mortalidade e o risco de superinfecção secundária. Da mesma maneira que as manifestações viscerais, as neurológicas são tratadas por benzimidazólicos, mais freqüentemente albendazole, corticosteróides ou dietilcarbamazine. Se detectado e tratado precocemente, o prognóstico das manifestações neurológicas da toxocaríase é favorável.

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