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Mini review

THE NEW CASES OF THELAZIOSIS ON THE BALKAN PENINSULA

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Abstract

Thelazia callipaeda (Spirurida, Thelaziidae), known as oriental eyeworm, is a parasite infesting the eyes of many domestic and wild carnivores which can also cause human infections. Due to the fact that infections by *T. callipaeda* have been recently spreading through the Balkan Peninsula, the main aims of this mini review are to give a clear and concise overview of the clinical manifestations, diagnosis and treatment of thelasiosis in animals and humans as well as to update epidemiological data about thelaziosis in this area. Clinical manifestations of thelaziosis can vary from subclinical to severe. In both animals and humans, treatment of thelaziosis can be effectively achieved with the removal of the nematodes from the eye under local anesthesia using a cotton swab or fine forceps. In the treatment of animals, antiparasitic drugs should be used supplementarily to the mechanical removal of parasites, while in humans, the topical use of antibiotics is desirable in order to prevent secondary bacterial infection. The growing number of diagnosed thelasiosis cases in dogs in the Balkan Peninsula, and particularly among owned pets in urban areas of Serbia previously considered free of infection, indicates

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the spread of zoonotic *T. callipaeda* in the area and in close proximity to humans. Finally, cooperation between veterinarians and physicians is strongly advocated in favour of the development of effective preventive measures and strategies.

Key words: diagnosis, epidemiology, Thelaziosis, treatment

INTRODUCTION

In Europe, *Thelazia callipaeda* (Spirurida, Thelaziidae), known as oriental eyeworm, is recognized as an eye parasite of many domestic and wild animals. The worm has been isolated from the eyes of dogs, cats, red foxes, wolves, beech martens, wild cats, golden jackals, lagomorphs and other animal species (Otranto et al., 2020). In addition, humans cases have been identified (Otranto & Dutto, 2008), while in the United States, another two species, *Thelazia californiensis* and *Thelazia gulosa* (the cattle eye worm), are involved in human infections (Bradbury et al., 2019).

T. callipaeda is transmitted to the vertebrate host by secretophagous fruit flies of the genus *Phortica* (Diptera, Drosophilidae) that feed on the tears of animals and humans (Otranto et al., 2005). During their meal, these fruit flies deposit the infective third stage larvae in the conjunctival sac of the vertebrate host and these larvae develop into the adult form in 35 days (Otranto et al., 2005; Maca & Otranto, 2014). After fertilization, *T. callipaeda* adult females release first stage larvae in the conjunctival sac of the final host, which can then be ingested by *Phortica variegata* in which they develop into the second (L2) and the third (L3) larval stage (Otranto et al., 2005). The L3 migrate to the labella and can be transferred to the host while flies feed on the eye surface, thus completing the parasite's life cycle (Otranto et al., 2006). Without treatment, adult worms can persist up to one year in the conjunctival sac, under the lids (Otranto et al., 2004).

Clinical manifestation, diagnosis and treatment of thelaziosis in dogs

Thelaziosis in dogs and other animals varies in its clinical manifestations from subclinical infection to severe ocular parasitosis. Some of the common clinical manifestations include conjunctivitis, epiphora, photophobia, mucopurulent ocular discharge, and occasionally keratitis, corneal opacity and corneal ulceration that can lead to blindness (Marino et al., 2020). Diagnosis of thelaziosis is generally simple and can be achieved by the observation of the eye, and particularly the surface of the cornea, the conjunctiva and under the eyelids and the nictitating membrane. The adult parasites are white, motile nematodes, visible by the naked eye (males measure 0.7–1.28 cm and females 1.1–1.8 mm in length) (Otranto et al., 2003). Nevertheless, if the parasites are in their larval stages, they are not easily detectable, and so lavage of the conjunctival sac and microscopic observation of the material can be required (Pimenta et al., 2013).

Treatment of thelaziosis can be effectively achieved with the removal of the nematodes from the eye (Lia et al., 2004). In that case, local anaesthesia is necessary and the parasites are removed using a cotton swab or fine forceps. Topical antibiotic treatment is also usually recommended in order to prevent or treat secondary bacterial infections (Diakou et al 2015). In addition, formulations containing macrocyclic lactones have been proven effective against the parasite and should be used supplementarily to the mechanical removal of the worms, as some parasites could remain (do Vale et al., 2019; Otranto et al., 2019). Milbemycin oxime (in a formulation with praziquantel) at the dose of 0.5 mg/kg administered orally twice, seven days apart, is licensed for treatment of infected dogs (Motta et al., 2012). Similarly, 2.5% moxidectin in a topical, spot-on formulation with 10% imidacloprid administered topically is licenced against *T. callipaeda* infection (Otranto et al., 2016; 2019). Furthermore, ivermectin off-label administration has been proven effective according to two reports (Pimenta et al., 2013; Diakou et al., 2015), while off-label local instillation of antiparasitic drugs (Lia et al., 2004) although displaying good results, is not practical due to the animals requiring restraint (Bianciardi & Otranto, 2005).

Prevention of the infection in dogs in endemic areas is very important, both for the protection of the animals and for the prevention of human infection. Milbemycin oxime showed 90-100% efficacy in reducing *T. callipaeda* infection rates when applied in a monthly prophylactic scheme (Ferroglio et al., 2008; Lebon et al., 2019). Similarly, monthly application of 2.5% moxidectin in a spot on formulation also containing 10% imidacloprid was highly effective in preventing *T. callipaeda* infection in dogs living in a highly endemic area (Lechat et al., 2015). Furthermore, the administration of a sustained-release formulation of moxidectin at the dose of 0.17 mg/kg resulted in full-season protection of the exposed dogs (Rossi et al., 2007).

Clinical manifestation, diagnosis and treatment of human thelaziosis

Since the adult worm can inhabit the orbit, conjunctival sac, or tear ducts (Chowdhury et al., 2018), the most common ophthalmic manifestation of human thelaziosis is conjunctivitis. Generally, symptoms of this parasitosis include increased lacrimation, itching, foreign body sensation, watery to mucopurulent discharge and photophobia (Otranto et al., 2020). However, other specific symptoms, such as visual acuity reduction and the presence of sensation that a black shadow moves in front of the eye (movement of the worm over the cornea) in anamnesis of some patients have been also described (Sharma et al., 2019).

Conjunctival hyperaemia, follicles and/or papillae in the tarsal conjunctiva, suffusion and corneal oedema are the most frequent manifestations that can be followed by keratitis or corneal ulcer, infiltration and inflammation of the lacrimal duct, corneal perforation and possible blindness in severe cases (Fuentes et al., 2011). Due to constant and long-lasting irritation, the palpebral conjunctiva can show follicular hypertrophy,

as well as a tarsal reaction. Moreover, *T. callipaeda* can also cause severe damage to the posterior segment of the eye and even detachment of the retina (Koka et al., 2019).

The suggested therapeutic treatment includes firstly rinsing the conjunctival sac with a five percent solution of povidone iodide for 3 min, followed by a rich rinsing with Ringer's lactate (Sharma et al., 2019). Treatment of thelaziosis is based on manual removal of the nematodes directly from the eye (conjunctival sac) with tweezers or a cotton swab, under topical anesthesia. After that, the use of antibiotic drops (tobramycin) is desirable in order to prevent secondary bacterial infection (Jirku et al., 2020). To date, there are no published data describing the systemic use of antihelmintic drugs after mechanical removal of eyeworm in the case of ocular infection in humans.

The worm is often localized in conjunctival fornix and therefore can be easily detected during an ophthalmological examination. In patients suspected of having helminthic infection, the identification of the infective agent, *Thelazia* sp., is simple by parasitological analyses – morphological and morphometric studies of the worm (Otranto et al., 2003). Although the third stage larvae develop into the adult form within 35 days in ocular cavities (Otranto & Dutto, 2008), in some cases, immature worms without specific morphological characteristics are removed from patients which makes parasitological diagnosis and identification impossible. Moreover, diagnosis in humans can be complicated due to the presence of clinical signs of an inflammatory response that is similar to allergic conjunctivitis than can lead the clinician to misdiagnosis (Otranto et al., 2003). Molecular analyses allow the detection and the identification of any developmental stage of worms and, therefore, are very helpful in diagnostic procedures (Otranto et al., 2005).

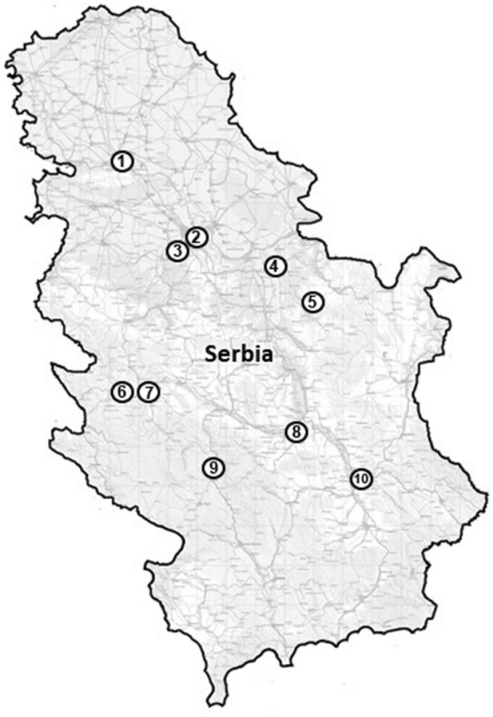
Epidemiological data

In Europe, there are data of autochthonous thelaziosis in animals in many countries, including Italy, France, Spain, Portugal, Austria, Switzerland, Germany, Greece, Slovakia and Hungary (do Vale et al., 2019; Otranto et al., 2020). Although more than 1000 cases have been reported to date in humans from different countries in Asia, only 10 cases have been described in Europe (do Valea et al., 2019). Recently, infection by *T. callipaeda* is spreading through the Balkan Peninsula, possibly due to armed conflicts that caused migration of domestic and wild animals and economic recession in the past 30 years as well as the presence of the vectors for this nematode in specific regions. Also, it is important to point out that cases of human thelaziosis have been reported in areas with high infection rates in animals (Colella et al., 2016). Based on the international literature and in chronological order, the first reports of thelaziosis in dogs were from the Western Balkans and Croatia, where interestingly, a human case has also been described (Hodžić et al., 2014; Tomić-Paradžik et al., 2016). In a neighbouring country, Bosnia and Herzegovina, *T. callipaeda* has been found in red foxes, dogs and cats (Hodžić et al., 2014). The first autochthonous case of thelaziosis in Greece was described in a dog living in a northern area of the country (Diakou et al.,

2015). Later, additional cases have been reported in animals from north-central Greece (Papadopoulos et al., 2018). Although to date there have been no further reports of cases in Greece, anecdotal reports from vets (through personal communication or in social media) indicate that the infection is more common than previously evidenced (Diakou, unpublished data).

In the Eastern Balkans and more precisely Bulgaria, this nematode has been identified only in dogs (Colella et al., 2016). The highest number of cases and a wider range of host species were noted in Romania, where the eyeworm was reported as parasite of dogs, cats, wolves, red foxes, and recently, mustelids (do Valea et al., 2019; Ionică et al., 2019).

In Serbia the first thelaziosis cases were reported in 2014 in dogs and cats (Gajić et al., 2014). Two years after the first evidence of this parasitosis in animals, a human case of thelasiosis was described (Tasić-Otašević et al., 2016). This was followed by evidence of *T. callipaeda* infection in foxes (do Valea et al., 2019).



1. Novi Sad - new cases in dogs 2018-2020
2. Beograd (red foxes; Pavlović et al. 2017)
3. Umka (cat; Gajić et al. 2014);
4. Požarevac (red foxes; Pavlović et al. 2017)
5. Kladurovo (dog; Gajić et al. 2014)
6. Užice (dog; Gajić et al. 2014)
7. Požega (dog; Gajić et al. 2014)
8. Kruševac (cat; unpubished 2014)
9. Brvenik (dog; Gajić et al. 2014)
10. Niš (2 cases in dogs in 2016 and **one new case in dog in 2019)**

Figure 1. Geographic locations of detected animal cases of thelaziosis in Serbia (newer cases are in bold)

Wild canids (such as foxes, beech martens, wolves) and felids, since they inhabit forested, meadow and hilly areas and environments characterized by high relative humidity and undergrowth, are exposed to the vector and could be definitive hosts for *T. callipaeda in both* endemic and non-endemic areas. Also, it is important to emphasize that foxes and wolves are predominantly active during dawn and dusk, parts of the day when vector is prevalent during summer months, thus contributing to the dissemination of thelaziosis within their natural territorial ranges from 10 to 30 km and up to 800 km, respectively (Otranto & Deplazes, 2019).

Herein, we report several new cases of thelaziosis in dogs from Serbia with the first reports of this parasitosis in the north of the country (Figure 1). From 2018 to date, 20 new cases of thelaziosis in dogs were diagnosed in Novi Sad (north Serbia) and one case in Niš city (south east Serbia), in a district where the presence of the parasite in dogs was already known (Tasić-Otašević et al., 2016). In Novi Sad, all infections of *T. callipaeda* were diagnosed in pets during visits to veterinary practices. Eyeworms were extirpated from 14 male and 6 female dogs, 2-10 years old. Based on their morphological and morphometric characteristics (Otranto et al., 2003), the worms were identified as *T. callipaeda.*

Additionally, in the last three years, one more case of thelaziosis was detected in a dog from south-east Serbia. During a clinical examination within a control program for stray dogs, in one female dog (3 years of age), ocular infection by *T. callipaeda* was diagnosed. In total, 48 worms were extracted from the dog's eyes of which 5 female and 5 male worms were morphometrically identified using software Image J (version 1.49i, National Institutes of Health, USA). Dimensions for female worms were 15.2-16.7 mm in length and 340 x 450 μm in width, while male worms were 9.7-13.3 mm in length and 300 x 360 μm in width.

CONCLUSION

The growing number of diagnosed thelaziosis cases in dogs in Balkan Peninsula and particularly among owned pets in urban areas of Serbia previously considered free of infection indicates the spread of zoonotic *T. callipaeda* in the area and in close proximity to humans. Better monitoring and timely diagnosis and treatment of infected animals (Diakou, 2017; Otranto & Deplazes, 2019), as well as an efficacious system of recording of cases, through improved links between veterinarians and human doctors under the One Health approach, could be the next step in designing preventive measures and strategies.

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Authors' contributions

S.T.O. and A.D. participated in study design and conception, wrote the manuscript and critically revised the manuscript. S.S. and A.D. were involved in acquisition, analysis, and interpretation of veterinary data. S.M. searched the literature, wrote and revised the manuscript. M.T. participated in the writing of the section on clinical manifestations, diagnosis and treatment of human thelaziosis. All authors gave final approval of the manuscript to be published.

Competing interests

Authors declare no conflict of interest.

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NOVI SLUČAJEVI TELAZIOZE NA TERITORIJI BALKANSKOG POLUOSTRVA

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TRENKIĆ Marija, DIAKOU Anastasia

Kratak sadržaj

Thelazia (T.) callipaeda (Spirurida, Thelaziidae), parazit oka mnogih životinja, može da izazove infekciju i kod ljudi. Činjenica je da je infekcija izazvana vrstom *T. callipaeda* počela da se širi teritorijom Balkanskog poluostrva nedavno i zbog toga je glavni cilj ovog mini preglednog rada da pruži jasan i koncizan prikaz kliničke manifestacije, dijagnoze i terapije telazioze kod životinja i ljudi, kao i da predstavi nove epidemiološke podatke o telaziozi ovog područja. Klinička manifestacija telazioze može da varira od subkliničke do vrlo teške forme. Kod ljudi, kao i kod životinja, terapija telazioze, koja podrazumeva uklanjanje nematode iz oka pod lokalnom anestezijom upoterbom brisa ili fine pincete, može biti sasvim dovoljna i efikasna. U lečenju životinja, primenjue se dodatno i tretman antiparazitskim lekovima nakon mehaničkog uklanjanja parazita, dok se kod ljudi preporučuje upotreba antibiotskih kapi da bi se sprečile sekundarne bakterijske infekcije. Na Balkanskom poluostrvu je primećen porast broja dijagnostikovanih slučajeva telazioze kod pasa, pogotovo kod vlasničkih pasa u urbanim regijama u Srbiji, koje su u prethodnom periodu smatrane područjima bez prisustva ove parazitoze. Saradnja veterinara i lekara bi mogla da obezbedi uspostavljanje efikasnih preventivnih mera i strategije protiv širenja ove parazitske infekcije.

Ključne reči*:* dijagnostika, epidemiologija, telazioza, terapija