POLISH HYPERBARIC RESEARCH 3(84)2023
Journal of Polish Hyperbaric Medicine and Technology Society

MEDICAL SIGNIFICANCE OF NEMATODES

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ABSTRACT

Nematodes are invertebrates that can cause parasitic diseases in humans, animals and plants. These organisms also participate in the decomposition of dead remains of organisms. In recent years, new reports have appeared on the possibility of using intentional nematode infections in the treatment of autoimmune and neurological diseases.
The aim of this work is to summarize information about nematodes pathogenic to humans and the possibilities of therapeutic use of some nematodes.
36 original and review publications from 2008-2022 were analyzed.
Information was collected on 13 diseases caused by parasitic nematodes in humans (reservoir, routes of infection, susceptible organisms, symptoms of infection). Current publications on trials of using *Trichuris suis* eggs (TSO) in animal models, in healthy humans and in people with inflammatory bowel diseases (IBD) or autism spectrum disorder (ASD) or multiple sclerosis (MS) are summarized. Clinical improvement was observed in some of the subjects. However, researchers draw attention to the depletion of the biodiversity of the host's intestinal microbiota in the presence of TSO.
Conclusions
The results of research on the therapeutic use of TSO remain inconclusive.
There are many more diseases caused by parasitic nematodes in humans than there are documented therapeutic effects of TSOs.
Exposure to parasitic nematodes' eggs (especially *Toxocara canis* and *Toxocara cati*) is still very common.
Keywords: nematodes, parasites, immunomodulation.

ARTICLE INFO

PolHypRes 2023 Vol. 84 Issue 3 pp. 41 – 56
ISSN: 1734-7009 **eISSN:** 2084-0535
DOI: 10.2478/phr-2023-0015
Pages: 16, figures: 0, tables: 0
page www of the periodical: www.phr.net.pl

Publisher
Polish Hyperbaric Medicine and Technology Society

Rewiev article

Submission date: 11.02.2023 r.
Acceptance for print: 20.02.2023 r.

INTRODUCTION

Nematodes (roundworms), a group with 27,000 described species. Their living environment may be decaying matter, soil, seas, fresh waters, and parasites live in the bodies of animals and plants. The nematode *Caenorhabditis* elegans was the first invertebrate to have its genome sequenced and its 19,000 genes fully described. Nematodes can cause parasitic diseases in humans, animals and plants. These organisms also participate in metabolism and energy circulation in the biosphere. In one rotten apple there are 90,000 nematodes that decompose them. These organisms have an elongated body shape (length from 200μm to 9cm), round in cross-section. Their body is unsegmented. They have three layers of coatings: hard, thick, flexible cuticle, syncytial hypodermis, and longitudinal muscles. They are covered with a cuticle that is resistant to chemical (digestive enzymes) and physical factors. They have a body cavity (pseudocoeloma). They do not have a circulatory system or blood. The nervous system is poorly developed; it consists of nerve trunks and a periesophageal ring instead of a brain; sensory structures are sensory papillae or chemical-receiving cavities at the ends of the body. Digestive system is a mouth sucking semi-liquid food, daggers may be present, intestine, anus closed by a strong sphincter.

They are characterized by anaerobic respiration: it consists in partial decomposition of glycogen; where there is oxygen, it diffuses into the interior of the animal's body. Excretion is carried out by two large cells running along the animal's body, connected by a transverse excretory canal ending with a hole. Nematodes reproduce sexually, and they do not regenerate or pack. Most often they are dioecious organisms. Fertilization is internal. Sperm without flagella crawl due to contractile skeletal proteins. The eggs are zygotes or early embryos. Sexually immature individuals hatch from them. Their bodies are miniatures of adults. Growth is interrupted by molting. Interestingly, nematodes are characterized by high internal hydrostatic pressure (40-400 cm of water column, i.e. 6.6-37.6 kN/m2) and a constant number of cells with a predetermined purpose in the body. Nematodes have the ability to actively move. Movement is caused by the contraction of 4 bands of longitudinal muscles, there are no circular muscles, each half of a given section of the nematode contracts and relaxes alternately, coordination of movement is possible thanks to the hydraulics of the fluid filling the body cavity [1].

Because of fluid's ability to flow, it transmits a force uniformly in all directions. The pressure at any point in a fluid at rest is the same in all directions. A fluid in a container exerts a force on all parts of the container in contact with the fluid. A fluid also exerts a force on any object immersed in it. The pressure in a fluid increases with depth because of the weight of the fluid above. Pascal's principle explains that in an incompressible fluid the increase in the pressure at any point is transmitted to all other points in the liquid undiminished. For animals like nematodae have a hydrostatic skeleton. They are soft-bodied animals lacking a bony skeleton. They utilize Pascal's principle to produce body motion. The structure means by which this is done is called the hydrostatic skeleton. To understand the movement of the animal such as a worm we can depict it as consisting of a closed elastic cylinder filled with a liquid. The animal produces its movements with the longitudinal muscles. Because the volume of the liquid in the cylinder is constant, contraction of the longitudinal muscles make the animal's body shorter and fatter. Longitudinal contraction on one side changes the direction of the motion. If there were circular muscles, their contraction would make the animal thinner and longer [2].

There are numerous publications on the negative health effects of nematodes in the body of humans, animals or plants. In recent years, new reports have appeared on the possibility of using intentional nematode infections in the treatment of autoimmune and neurological diseases.

THE AIM

The aim of this work is to summarize information about nematodes pathogenic to humans and the possibilities of therapeutic use of some nematodes.

METHODS

36 original and review publications from 2008-2022 were analyzed.

RESULTS AND DISCUSSION

Descriptions of 13 diseases caused by nematodes were found in the medical literature: Filariasis, ascariasis, loa-loa, onchocerciasis, pinworms, trichinosis, whipworms, strongyloidiasis, thoriasis, anisakiasis, trichostrongylosis, drecunculiasis and toxocariasis. We also found 13 publications on the potentially therapeutic use of nematodes in patients with allergies, immune disorders and autoimmune diseases.

Filariasis (vusheriosis) is caused by *Wuchereria bancrofti*. Brugiosis and *Brugia malayi, Brugia timori (filariasis)*. Their vector are mosquitoes of the following species: *Culex, Aedes, Anopheles*. The reservoirs are humans, monkeys and cats. In Europe there are: *Dirofilaria repens, D. Immitans, D. ursi. D.* repens is a parasite of dogs and foxes. *D. immitans*-dogs, cats and beavers. Bears are hosts to *D. ursi*. In the blood of these mammals there are microfilariae, which are the first larval stage of filariasis. Mature forms of nematodes live in lymph nodes and vessels. Clinical symptoms of Filariasis include inflammation of lymphatic vessels and nodes, testicles, epididymis, fever, arthritis, sterile abscesses, elephantiasis, testicular hydrocele, lacturia, cough, shortness of breath, hemoptysis, and low-grade fever. Eye invasions do occur. The parasite can be located in the eye socket, eyelid, conjunctiva or vitreous body. The most common symptoms are swelling eyelid or drooping. This can lead to eye damage, glaucoma, retinal detachment. Surgical attempts to remove the filaria from the eyeball can lead to damage to the optic nerve. *Dirofilaria sp.* microfilariae can cause enlargement of lymph nodes, formation of necrotic changes in vessels. In laboratory tests, eosinophilia is typical. There are no specific serological tests to detect *Dirofilaria sp.* infection. The diagnosis is made on the basis of histopathological evaluation [3,4].

Ascariasis caused by *Acaris lumbricoides*. The disease may be asymptomatic or with symptoms of

asthma and alveolitis during the migration of larvae (LÖffler syndrome - eosinophil infiltration, eosinophilia in the blood). Complications may include intestinal and bile duct obstruction, liver enlargement, fever, cough, skin rashes, skin itching, abdominal pain, nausea, vomiting, constipation, lactose intolerance, malnutrition, pain, dizziness, fainting, convulsions, insomnia, apathy, excitability, nightmares, conjunctivitis, tearing, dry cough. The ailments are related to the migration of the larvae first from the digestive tract through the blood vessels to the lungs, where they molt, then are swallowed and reach the adult form in the small intestine. Coproscopic examination allows the detection of human roundworm eggs in a fecal smear. Adults reach a size of 20-35 cm in the case of females and 30 cm in the case of males. The female lays up to 200,000 eggs a day. They reach the invasive stage when they are excreted with feces in the soil in humid conditions at a temperature of 25°C and mature for 2-3 weeks. It enters the human body through the digestive route. The reservoir is humans [3,5].

Loa-loa is a disease caused by the *Loa loa* nematode from the family *Filarioidea* (Loiasis). The nematodes migrate in the subcutaneous tissue of the infected person, causing skin erythema and swelling around the ankles, wrists, and sometimes the face and torso. The worm travels under the conjunctiva of the eye and causes pain and swelling in the eye socket. The diagnosis is made by detecting microfilariae in blood smears. The female lays larvae (microfilariae), which enter the blood. Circulated during the afternoon hours, showing daily periodicity. The reservoir is humans, and the vector is flies of the genus *Chrysops (C. dimidiata, C. silacea, C. distinctipennis*) infected with invasive nematode larvae. The entry point of infection is the skin. A person can infect a carrier while microfilariae are present in the blood for many years. When flies suck blood, the larvae enter human skin. Then into the subcutaneous tissue. There they reach maturity after 5 months [3,6].

Onchorerciasis is a disease caused by the nematodes *Onchocerca volvulus*, which live in the skin and subcutaneous tissue, causing nodules in the affected areas. The reservoir of the parasite is humans, who infect the carriers for as long as the microfilariae are present in the skin, which lasts for many years. The parasite is transmitted by blood-sucking flies of the genus *Simulium* (black-fly) *(S. Ochraceum, S.callidum, S.metallicum, S.exiguum, S. guyanense, S. neavei)* infected with invasive nematode larvae that live near rivers. At a temperature of 21-24°C, the parasite develops in the vector's body to an infective form for humans within 6 days. An adult blackfly lives for about 2 weeks, and sometimes even 10 weeks. While sucking blood, microfilariae enter the midge's stomach. They penetrate the muscles. Over there they reach the invasive stage and return to the insect's mouthparts. During subsequent sucking, the parasites enter the human skin and develop into adults within a few months. Humans become infected when a female midge stings the skin to draw blood. It then introduces invasive microfilariae into the subcutaneous tissue. There they continue to develop until they reach sexual maturity. Microfilariae can develop in the skin of the entire human body and in the eyeball. The female gives birth to microfilariae, which cause the formation of subcutaneous nodules. Invasion of the eyeball by microfilariae causes inflammation of the conjunctiva, choroid, retina and damage to the cornea. Microfilariae survive in the human body for 1-2 years. The stings of the midges cause red itchy lesions on the skin. Microfilariae in the skin cause discoloration and discoloration of the skin with itching,eczema, swelling, loss of skin elasticity, which is referred to as "lizard skin". The skin discoloration in this disease is called "leopard skin". Adult roundworms form painless tumors in the subcutaneous tissue. The cause of skin lesions is the death of microfilariae there and the accompanying inflammation.

The inguinal lymph nodes may become enlarged. Chronic inflammation of the lymph nodes leads to obstruction of the lymphatic vessels and the formation of edema or elephantiasis of the lower limbs. Eosinophilia is found in the blood. In some patients, onchocerciasis causes weight loss and musculoskeletal pain. Accidental migration of nematodes to the central nervous system causes paresis, paralysis and epileptic seizures, and delays physical development and sexual maturation in children. In response to the presence of microfilariae, punctate keratitis may occur. Sometimes sclerosing inflammation of the cornea develops, causing massive scarring, which causes amblyopia, "river blindness." The most dangerous complications of onchocerclosis are permanent clouding of the cornea, damage to the optic nerve, inflammation of the iris and ciliary body, and retinitis. The diagnosis can be made based on the presence of motile microfilariae in a skin biopsy. Biopsies are taken superficially (0.5-1 mm). Differentiation from other species is possible using Giemsa staining. Sometimes motile microfilariae can be detected during a slit lamp examination of the eye. The Mazzotti skin test involves observing the severity of skin symptoms of the disease after administering a small dose of diethylcarbazine, which induces the breakdown of microfilariae in the skin. Within 20 minutes of administration of the drug, an increase in pruritus and rash is observed. A positive result of the Mazzotti reaction is the basis for continuing treatment of onchocerciasis [3,7].

Enterobiasis is an invasive disease of the large intestine caused by the nematode *Enterobius* vermicularis. It most often occurs in children, causing: anal itching, pain, nausea, loss of appetite, hyperactivity, insomnia, bedwetting, and inflammation of the large intestine. Adult females can migrate to the vagina, uterus, and fallopian tubes, causing vaginitis, vaginal discharge, and vaginal bleeding before puberty. Detection involves detecting eggs or adult roundworms in the anal area. The material is collected using the cellophane adhesive method. Sometimes the disease is asymptomatic. Sometimes you can notice white worms 9-12 mm long around the anus. Pinworm is a nematode found only in humans. After humans swallow the parasite eggs, they travel through the digestive tract to the small intestine. After two molts, the worms enter the large intestine, where, after another molt, they reach adulthood. Copulation takes place in the large intestine. The female lays eggs on the skin around the anus at night. Within 6 hours, the egg becomes invasive at a temperature of 30-36°C. The reservoir is humans. It is spread through the oral route by moving into the mouth and swallowing eggs from contaminated bedding, underwear, towels, toys and food. Children may be subject to reinvasion due to finger sucking. Nail biting increases the risk of infection. The infestation can be spread by inhalation when pinworm eggs are suspended in dust. The portal of infection is the oral cavity. Incubation period 2-4 weeks. Excretion of the pathogen - through the anus. In Poland, it occurs in

several percent of adults and several dozen percent of children [3,8].

Trichinosis is a parasitic zoonosis caused by nematodes of *the Trichinella genus* (*T. spiralia, T. nativa, T.britovi, T. nelson, T.murelli, T. Pseudospiralis*). Symptoms of the disease include muscle pain, fever, eyelid swelling, conjunctival ecchymosis, subungual ecchymosis, sometimes diarrhea, vomiting, abdominal pain, and may even lead to myocarditis. The disease is accompanied by eosinophilia in laboratory tests. Eosinophilia increases between the 2nd and 5th week of invasion. The diagnosis is confirmed by the increase in the titer of antibodies against Trichinella sp. in the blood serum and the detection of parasite larvae in muscle tissue. After eating meat infected with larvae, they penetrate the intestinal villi in the human small intestine. They reach sexual maturity in the mucous membrane of the digestive tract. After conjugation, second generation larvae are born. These larvae penetrate the blood vessels, are carried with venous blood to the right half of the heart, then to the lungs, and then they can reach all organs and tissues. They permanently settle in striated muscles. The larvae that have grown in the muscles and molted twist. The encysted larvae can survive for several years. The capsule surrounding the larva becomes encrusted with calcium salts. The reservoirs are carnivores and omnivores, most often wild boars, wolves, brown bears, polar bears, red foxes and raccoon dogs. On the farm it may be a pig or fur animals. The source of infection is raw and semi-raw meat from carcasses of animals infected with *Trichinella sp.* It is often pork. The portals of infection are the oral cavity and the digestive tract [3,9].

Trichuriasis is an invasive disease of the large intestine caused by the nematode *Trichiuris trichiura*. It is often asymptomatic and sometimes causes abdominal pain, diarrhea, constipation, acidic stools, rectal prolapse, weight loss, anemia, and growth retardation in children. It is detected by microscopic examination of feces for the presence of eggs. Flotation techniques are recommended. Adult parasites can be detected by colonoscopy. The front part of the worm's body is stuck in the intestinal mucosa and causes bleeding, while the rear part of the body remains in the intestinal lumen. The reservoir of the parasite are human. The source is food and objects contaminated with parasite eggs. The eggs are excreted in the feces. They get into the soil, where under appropriate conditions they become infested eggs and remain infective for a year. Fertilizing crops with human feces and eating unwashed fruit and vegetables contribute to infection. Path of infection - through the mouth with water, food, dirty hands, objects placed in the mouth. The period of incubation from the swallowing of invasive eggs to the appearance of sexually mature individuals lasts 60-70 days. Adult forms can survive in the intestine for up to 8 years [3,10].

Strongyloidiasis is an invasive disease of the duodenum and small intestine caused by nematodes of the *Strongyloides genus* (*Strongyloides stercoralis, Strongyloides fulleborni, Strongyloides fulleborni kellyi).* Strongyloides in the form of rhabditoid larvae transform into invasive larvae in the external development cycle. Invasive larvae enter the host's body by penetrating the skin, then enter the small intestine through the lungs, bronchi and glottis. Females and males reach maturity in the small intestine. After fertilization, the females burrow into the mucous membrane of the small intestine, lay eggs there, and larvae develop from them. They enter the intestinal lumen, where they transform into rhabditoid larvae, which are excreted in the feces. In the external cycle they reach maturity. If, during molting, the rhabditoid larva transforms into a filario-like larva, it can penetrate the intestinal wall and begin its journey in the host's body. The reservoir for *Strongyloides stercoralis* are humans and dogs, and for *Strongyloides fulleborni* - monkeys and humans. The source of infection is soil contaminated with feces. The route of spreading: invasive larvae actively penetrate the skin of people walking barefoot or working with bare hands in contaminated soil. Autoinvasion is possible. The gates of infection are the skin, rarely the mucous membranes for *Strongyloides stercoralis*, the oral cavity for *Strongyloides fulleborni* and *Strongyloides fulleborni kellyi*. The lodging period is 1 month. The parasites are excreted in the feces. In the case of *Strongyloides fulleborni* and *Strongyloides fulleborni kellyi* infections also *via* breast milk. Some cases are asymptomatic, skin changes may occur: itchy blotchy redness, petechiae - periodically during the penetration of the larvae through the skin and in the case of chronic migration of the larvae in the subcutaneous tissue. In cases of larval migration through the lungs, there is a cough, fever, pneumonia. Sometimes there are diarrhea, abdominal pain, loss of appetite, weakness, vomiting, bloody stools. Laboratory tests show leukocytosis and eosinophilia. Diagnosis can be made based on the detection of viable larvae in feces, duodenal contents or sputum. Parasite eggs can be detected in the feces and milk of breastfeeding mothers. Serological tests can also be performed - specific IgG antibodies [3,11].

Hookworm (*ankylostomosis, necatorosis*) is a parasitic disease of the duodenum, jejunum, and ileum caused by *Necator* and *Ancylostoma species*. They develop in humans and some species of monkeys (gorillas, mandrills). Hookworms are geohelminths. Their developmental forms require incubation in the soil under favorable climatic conditions. They can occur in tropical countries, and in countries with a temperate climate in mines, caissons, brickworks and underground tunnels. Of epidemiological importance are the hookworm *Ancylostoma duodenale* and the American hookworm *Necator americanus*. Female hookworms live in the human small intestine, where they lay eggs (25-35,000 per day). The female *Ancylostoma duodenale* survives in the intestine for 1-3 years. Female *Necator americanus* 3-10 years old. At a temperature of 23-30°C, with access to oxygen and high humidity, rhabdid larvae hatch from the eggs within 24 hours. They can survive up to 2 years in the soil. After a series of moults, the larvae develop into third-stage pillar-like larvae, which are motile and attach themselves to plants and may even attack hosts and penetrate their skin, most commonly through hair follicles. Then the larvae migrate with the blood to the right side of the heart, to the lungs, from the alveoli along with the movement of the gonococcal epithelium to the trachea and pharynx. Swallowed larvae enter the digestive tract, where they reach their mature form in the intestine. Humans become infected with invasive larvae from soil contaminated with human feces. The larvae actively penetrate through intact skin. Infection with *Ancylostoma duodenale* may also occur through the oral route with food or drink and in the case of geophagy. At the site of invasion, itchy lesions appear on the skin in the form of papules or pimples. The migration of larvae in the body causes eosinophilia. During the journey, inflammatory changes are formed in the lungs, shortness of breath, dry cough, expectoration of blood-colored

secretions, spastic bronchitis occur. Radiological imaging reveals LÖffler's infiltrates or bronchopneumonia. Mature parasites attach to the mucosa of the small intestine through their mouth pouches and feed on blood. In endoscopy, mucosal lesions caused by the parasite may resemble ulcers.

Clinical symptoms of infection include abdominal pain, loss of appetite, loose, tarry stools, and weakness. Laboratory tests reveal iron deficiency, hypoproteinemia, and weight loss. Complications may include heart failure, respiratory failure, retinitis, optic nerve inflammation, retinal hemorrhage, and even cognitive impairment. Diagnosis is possible based on the detection of larvae in fecal parasitological culture. Molecular testing can be used to identify the species [12].

Anisakiasis is a parasitic infection caused by zoonotic nematodes from the *Anisakidae* family: *Anisakis simpex, Anisakis pegreffi, Contracaecum spp., Terranova spp., Pseudoterranova spp., Phocanema spp*. Humans are an accidental host and become infected by eating raw fish or seafood dishes with invasive pathogens. parasite larvae. During its development, the parasite uses a final host (usually a large marine mammal) and two intermediate hosts - crustaceans and freshwater fish. In humans, larvae swallowed with fish reach sexual maturity in the stomach. The larvae can get into the muscles. People infected with *Anisakidae* develop damage to the stomach wall and sometimes duodenal stenosis. Where the larvae live, erosions, inflammatory changes, mucous membrane swelling, petechiae and eosinophilic infiltrates occur. After a few or several dozen hours after eating infected fish, severe abdominal pain, nausea and vomiting occur. Gastroscopy can reveal the larval forms of the roundworm. Accidentally, the larvae may migrate to the large intestine, causing ulcers, inflammatory infiltrates, perforations, and bloody diarrhea. Symptoms may persist for months or years. It may be accompanied by hives, itching, angioedema, bronchial spasms, and anaphylactic shock. In 60% of cases, increased leukocytosis, increased IgE, and specific antibodies are observed. The final diagnosis is made based on the morphological examination of nematodes removed from the gastrointestinal tract during endoscopic examination or histopathological examination of sections taken from the intestine. In the human body, the parasite does not complete the development cycle, as in marine mammals, so it is not possible to observe the eggs [13].

Trichostrongylosis is a zoonotic parasitic disease. Humans are an accidental host for nematodes of the genus *Trichostrongylus. Humans are infected by T. orientalis, T. colubriformis, T. probulurus, T.vitrinus, T. axei, T. skijabini, T. lerouxi, T. capriolola*. The roundworm develops in the mucous membrane of the duodenum and small intestine of herbivorous animals. The female lays eggs in the digestive tract of the final host. They are then expelled together with the first-stage larvae to the external environment, infecting the vegetation. Within a few days, under favorable climatic conditions, the parasite's eggs develop into rhabdiform larvae (second-degree larvae), and within another 5-10 days they develop into a larva (third-degree larvae). The source of human infection are green vegetables, herbs and tropical vegetables contaminated with farm animal feces. A vegetarian diet and the use of oriental spices promote infection. The larvae accidentally swallowed by humans grow up in the human small intestine, where they develop into adults. The filariasis-like larva of *Trichostrongylus sp*. can penetrate the human body through intact skin. The infected person excretes the invasive eggs in the feces. The infection is most often asymptomatic. Abdominal pain, loose stools, nausea, vomiting, flatulence, loss of appetite, weight loss, fatigue, headaches and dizziness may occur. Laboratory tests reveal eosinophilia, anemia, and leukocytosis. Some patients may experience shortness of breath, bronchial asthma, dry cough, and rash with itching. Rarely, biliary obstruction, cholecystitis, gastrointestinal bleeding. The disease is a serious veterinary problem in areas where goats and sheep are raised due to the increasing resistance of this parasite to antiparasitic drugs. The diagnosis of the disease is made by detecting the presence of its eggs in the stool [14].

Dracunculosis is a chronic fiolar disease of the skin and subcutaneous tissue caused by the *nematode Dracunculus medinensis*. The source of transmission in endemic areas are surface water reservoirs. The female measures up to 120 cm. After fertilization, it gives birth to hundreds of live larvae (microfilariae) into the aquatic environment. For 2-6 weeks. The larvae remain viable in water for 5-6 days. They are swallowed by an eyed crustacean of the genus *Cyclops*. The parasite further develops in its body to a stage that is invasive to the final host. People become infected accidentally by drinking water from open freshwater reservoirs contaminated with eyeworms. In the human stomach, the larvae are released under the influence of acid from gastric juice and travel through the wall of the digestive tract into the blood, lymph, and intestinal mesentery, where they mature. From there they enter the capillaries and then into the subcutaneous tissue of the lower limbs, where they develop into a mature form. The parasite reaches maturity after a year of living in the human body. Symptoms of dracunculosis include allergic and toxic eruptions related to the migration of the parasite, fever, malaise, headaches, nausea, vomiting, loose stools, abdominal pain, and hives-like eruptions. The localization of the parasite in the lower limbs is accompanied by erythema and eczema on the lower limbs with itching. Then blisters filled with milky fluid form around the ankle joints. Upon contact with cold water, the blisters burst and release live microfilariae into the environment, which the female gives birth to each time it comes into contact with water. Dead nematodes become a source of inflammatory and allergic lesions with swelling, erythema and necrosis. Inflammation of the surrounding joints may occur. The presence of live nematodes can be detected by ultrasound examination. Calcified dead parasites are visible on X-ray. High eosinophilia is found in the blood. Microfilariae can be detected in the milky fluid from the blisters on the feet [15].

Toxocarosis is a parasitic disease caused by nematodes of the genus *Toxocara*. They typically parasitize the bodies of cats and dogs, and human infection occurs accidentally after ingestion of invasive parasite eggs. In the human small intestine, larvae hatch from the eggs and then travel to various organs. This migration causes an inflammatory reaction. Therefore, the disease is referred to as visceral larva migrans syndrome. Man is an accidental host. Toxocariasis is transmitted by foxes, wolves, coyotes, felines, rabbits and poultry. Adult Toxocara live in the small intestine of dogs (*Toxocara canis*) and cats (*Toxocara cati*). After reaching maturity and fertilization, females lay eggs that are excreted in the faeces. The eggs mature in the soil. Under

favorable conditions, after 2-5 weeks, they become invasive eggs. Humans become infected by ingesting infective eggs with contaminated food or through dirtyhands. Infection is possible by inhalation of dust containing invasive eggs, by droplet contact with a sick animal. In the human small intestine, larvae are released from the invasive eggs, which penetrate the wall of the small intestine into the lumen of blood vessels and thus reach various organs. Most of it goes to the liver, so hepatimegaly is the more common symptom. Granulomas form in the liver. Some of the larvae enter through the right side of the heart with blood to the lungs. A few enter the general circulation and skeletal muscles, the central nervous system or the eye. Such larvae can survive in the human body for up to 10 years. However, they do not reach sexual maturity. Therefore, humans are not infectious to the environment. Dying larvae trigger an immune response, which leads to the formation of granulomas. The course of the disease may be asymptomatic, it may present as visceral larva migrans syndrome or as neurotoxocariasis.

Common symptoms include weakness, fatigue, lack of appetite, fever, sleep disturbances, muscle and joint pain, abdominal pain and headaches. If larvae are present in the lungs - cough, shortness of breath. If the eye is affected - vision disorders. Physical findings include hepatomegaly, splenomegaly, enlarged lymph nodes, rashes, papules, and erythema. If the larvae are present in the central nervous system, they may be located in the meninges, the white or gray matter of the brain, the cerebellum or the spinal cord. Symptoms of neurotoxocariasis include cognitive decline, personality disorders, and seizures. Sometimes meningitis or encephalitis. Laboratory tests reveal eosinophilia, increased transaminase activity, and hyperganmaglobulinemia.

Serolgical diagnosis involves the detection of specific IgG and IgE antibodies against *Toxocara* antigens in the blood using the ELISA method. Confirmatory tests are performed using Immunoblot methods. Sometimes the diagnosis is made after histopathological examination [16].

Recently published experimental work attempted to check whether parasitic nematodes can alleviate the symptoms of chronic inflammatory, allergic, neurological and autoimmune diseases.

The study by Jaeger et al. examined whether the presence of the whipworm *Trichuris suis* in the intestine of mammals (mice) would reduce inflammation typical of Crohn's disease (CD) in the ileum compared to placebo after 12 weeks. The effectiveness of such an intervention has not been proven. However, it has recently been shown that spontaneous inflammatory lesions of the small intestine in mice can be significantly ameliorated when these mice are colonized with *Trichuris muris* [17].

Sandborn and co-investigators also tested the effect of *Trichuris suis* (TSO) on intestinal inflammation in the course of inflammatory bowel disease (IBD) in humans. The safety and tolerability of TSO after a single dose was assessed in patients with Crohn's disease. After 2 months of the study, the most common patients reported gastrointestinal symptoms: 25.9% of patients treated with TSO and 33.3% of patients treated with placebo. The authors concluded that a single dose of *Trichuris suis* ova up to 7,500 ova was well tolerated and did not cause short- or long-term treatment-related side effects [18].

In turn, Schölmerich et al. studied the effectiveness and safety of three different doses of TSO in comparison with placebo on a group of 252 patients with Crohn's disease. Patients received a randomized dose of TSO every two weeks (250, 2500 or 7500 TSO/15 ml suspension/day) or 15 ml placebo. Clinical remission at week 12 was 38.5%, 35.2% and 47.2% of TSO 250, TSO 2500 and TSO 7500 patients, respectively, and 42.9% of placebo-treated patients. TSO induced a dose-dependent immune response. TSO did not affect blood inflammatory parameters. The authors concluded that administration of 250-7500 TSO every two weeks for 12 weeks was safe and produced a dose-dependent immune response [19].

Garg compared 2 clinical studies: one study evaluated the efficacy and safety of TSO cells in patients with ulcerative colitis (n = 54). The second study was a phase one study that evaluated the safety and tolerability of *T. suis* oocytes in patients with CD (n = 36). The study lasted 12 weeks. The subjects received portions of 2,500 TSO in 0.8 ml of physiological saline every 2 weeks. Ten percent of patients in the TSO group achieved remission compared with 4% in the placebo group. Forty-three percent of patients in the TSO group achieved clinical improvement compared with 17% of the control group. However, the authors cautiously summarized the study by admitting that the sample size was only 90 people and concluded that there is not enough evidence to draw firm conclusions regarding the efficacy and safety of the use of intestinal worms in the treatment of patients [20].

Huang et al. conducted a meta-analysis of randomized placebo-controlled clinical trials (RCTs) on the effects of TSOs in inflammatory bowel diseases. In ulcerative colitis, TSO has been studied in 3 RCTs involving 74 subjects. The rates of induced clinical remission and clinical response were 10.8% and 53.8% in the TSO group, while 6.7% and 29.0% in the placebo group. 22% of patients in the TSO group experienced at least 1 adverse event compared to 27.3% in the placebo group [relative risk (RR) 0.75, 95% confidence interval (95% CI) 0.17- 3.27]. In the analysis of CD studies, 3 RCTs involving 538 people were reviewed. In this category, 40.7% of patients in the TSO group achieved clinical remission compared to 42.9% in the placebo group (RR 0.95, 95% CI 0.75-1.20). The authors concluded this meta-analysis by stating that TSO did not provide a statistical benefit to patients with inflammatory bowel disease (IBD) [21].

While the cited studies were conducted in Europe and America, in 2021, researchers from Asia again attempted to assess the safety of using TSO on a group of 12 healthy Japanese volunteers from Tokyo. They received TSO 1000, 2500 or 7500 orally and were followed for 56 days. No serious adverse events were observed in either group during the study period. Three participants in the TSO 1000, 2500, and 7500 groups had mild to moderate abdominal symptoms, diarrhea, flatulence, and loss of appetite during the follow-up period. One participant in the placebo group developed mild diarrhea. Microscopic examination did not reveal the presence of parasite eggs in any stool sample. Blood tests showed elevated eosinophil counts in a few cases, especially in the groups receiving the higher dose of TSO. In all cases, there were no extra-abdominal symptoms. To summarize: healthy Japanese people tolerated all doses of TSO without any serious side effects. The authors suggest that the use of TSO in Japan is relatively safe and careful

monitoring of patients is recommended to ensure sustainable use [22].

Williams et al. tried to use endoxoscopic and laboratory methods to analyze what effects TSO causes in the body of a healthy male volunteer. TSO treatment induced *T. suis*-specific serum antibodies, transient blood eosinophilia, and an increase in the number of IFNγ + and IL4 + cells in the circulating CD4 + T cell population. Increased expression of genes encoding cytokines (IL4, IL10, IL17 and TGF-β) and transcription factors (FOXP3, GATA3 and RORC) was seen in the ascending and transverse colon (site of predilection for worms), while only limited changes in gene expression were observed in proximal ileum and distal (descending colon) to the infected tissue. The authors noted that the volunteer experienced a significant improvement in psoriasis while being treated with TSO. Thus, TSO treatment induced a mixed Th1/Th2/T regulatory response at the local site of infection, which was also reflected to some extent in the peripheral circulation [23]. This procedure was called colonization with medicinal nematodes [24].

In turn, Hollander et al. studied the effect of TSO on autism spectrum disorders (ASD) in 10 adults in an experiment lasting 28 weeks, hoping for a positive immunomodulatory effect of nematodes on the inflammatory mechanisms in these disorders. Large effects were observed in improving repetitive behaviors, restricted interests, rigidity and irritability. No changes were observed in the area of social communication. Differences between treatment groups did not reach the level of statistical significance. TSO caused only minimal, non-serious side effects [25]. However, Siniscalco et al. describe in their article why TSO, having strong immunomodulatory properties, may be useful in the treatment of immunological disorders associated with ASD [26]. Yordanova et al studied the effect of TSO on the cellular and humoral immune response in 5 patients with multiple sclerosis (*vs*. 6 receiving placebo). Patients received 2,500 TSO orally every 2 weeks for 12 months. However, the results were inconclusive [27]. It is worth remembering that experiments in an animal model to verify hypotheses on the effect of nematodes on the course of various diseases can be carried out on rodents, pigs and primates (using *Ascaris, Trichuris and Toxocara spp.*). The relationship between *Trichuris* and *Ascaris* nematodes and the microbiota is also emphasized [28].

Nematode infestation reduces the biodiversity of the host's gut flora [29]. It is worth noting that infections with parasitic nematodes are common in tropical countries, their risk in developed countries of temperate climate is also high. In studies conducted in Iran in 2014, *Toxocara sp.* eggs were detected in 29% of soil samples, [30], in 2019, 18% of samples (in the flotation test) [31]. In 2013, 7-16% of sand soil samples from Mexico tested positive for *Toxocara spp.* Eggs [32]. In Spain, more than 10% of soil samples from parks tested positive for *Toxocara spp.* eggs. In dog parks, more than 30% of the samples tested positive [33]. In Turkey, eggs of parasitic nematodes [34] were found in 55% of the parks surveyed. Pets accompanying humans (cats and dogs) very often carry parasitic nematodes. In the years 2000-2019, 68 articles were published on this topic, describing cases of infection with *Toxocara* nematodes in cats and dogs from China. Of the 24,490 dogs tested by fecal flotation, Toxocara was detected in 17% of them as well as in 22% of the 844 cats [35]. In Europe, however, the percentage of cats and dogs infected with *Toxocara* germs has not changed significantly and amounts to 14.6% of dogs (*Toxocara canis*) and 24.5% of cats (*Toxocara cati*) [36].

Hand hygiene remains the best method of preventing nematode infections.

CONCLUSIONS

The results of research on the therapeutic use of TSO remain inconclusive.

There are many more diseases caused by parasitic nematodes in humans than there are documented therapeutic effects of TSOs.

Exposure to parasitic roundworm eggs (especially *Toxocara canis* and *Toxocara cati*) is still very common.

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