# *E. VERMICULARIS* – PROSPECTS FOR FUTURE RESEARCH: A BRIEF LITERATURE REVIEW

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**ABSTRACT**

*Enterobius vermicularis* is an intestinal parasite with a cosmopolitan distribution and the disease which causes (enterobiasis) is one of the most common helminth infection worldwide. According to literature data it affects nearly 1 billion people and is found in various socio-economic groups. Everyone is susceptible to infection, but children are more often affected than adults due to their poorly developed hygiene habits. Patients with enterobiasis are often reinfected which together with the high endurance of the pinworm eggs in the environment contributes to the difficult control of the disease. In recent decades, a number of studies have been conducted on the genotypic characteristics of the nematode, including sequencing, which accumulates data on phylogenetic varieties of the species to improve the diagnosis and control of this infection in humans.

The available data reveal influence of *E. vermicularis* on the local immunity of intestinal mucosa in infected individuals, but these data are scarce and contradictory and do not clarify the significance of this influence on the clinical manifestations of the disease. Additional studies are needed to define the relationship of this effect with the clinical symptoms of the disease.

**Keywords:** *Enterobius vermicularis*, molecular characterization, *cox*1 gene, intestinal imbalance.

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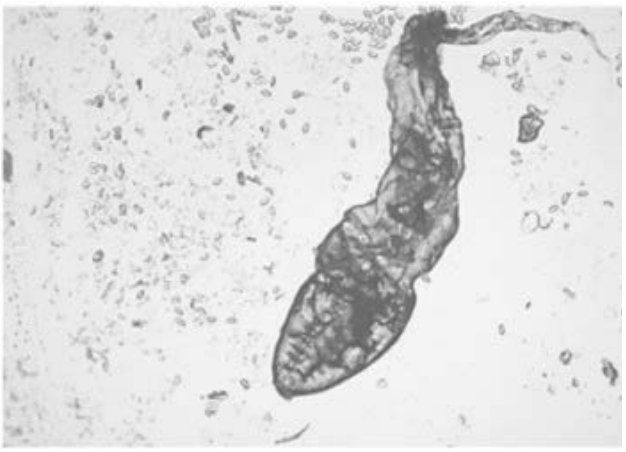
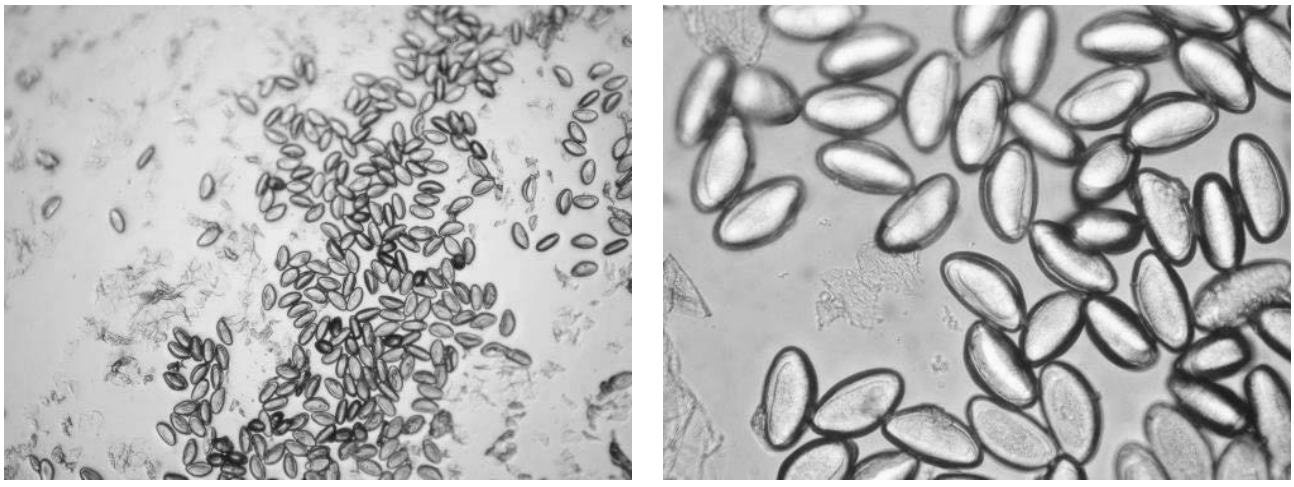


**Figure 1.** *Enterobius vermicularis* adult female (4x10) in scotch tape samples (The authors, 2022).

## ENTEROBIASIS

Causative agent is the small nematode *Enterobius vermicularis* (Linnaeus, 1758), which systematically belongs to phylum *Nematoda*, class *Rhabditea*, order *Oxyurata*, family *Oxyuridae*, genus *Enterobius*. *Enterobius vermicularis* (syn. *Oxyuris vermicularis*) is an obligate intestinal parasite. Adults are grayish-white in color, threadlike, with pointed edges. The male is 2-5 mm x 0.2 mm, with a curved tail end, and the female, 8-13 mm x 0.5 mm (Fig.1). The eggs are asymmetrical, measuring 50-60 x 20-30 µm (Fig.2), smooth, translucent, double-contoured with a five-layer shell, the inner one being fibrous and relatively impervious to chemicals. Their internal contents are larvae at different stages of development (1). Biological cycle takes place in two stages: parasitic (in hosts intestines) and non-parasitic (in perianal folds of the infected person and the environment). The pinworms inhabit lower parts of the small intestine and the upper parts of the large intestine. At night, they actively come out through the anus and lay their eggs in the perianal folds. In the presence of oxygen, moisture, and temperature of 37°C the eggs mature in 4-6 hours and become infective. The female lays between 10,000 and 17,000 eggs a day. The lifespan of pinworms is 3-4 weeks (2). The route of transmission is fecal-oral, through ingestion of infective eggs with contaminated food, when children put their toys or unwashed hands in the mouth and also by inhalation of dust contaminated with eggs which are subsequently swallowed. The pathogenic effect of pinworms is due to a mechanical injury



**A** **B**

**Figure 2.** *Enterobius vermicularis* eggs – A (10x10) and B (10x40) in scotch tape samples (The authors, 2022).

of the intestinal mucosa to which they attach. A granuloma consisting of eosinophils, lymphocytes, and macrophages forms at the site of attachment. The parasite provokes motor and secretory reflex responses of the digestive tract but also toxic and allergic reactions of the host organism (3). In general, enteriobiàsis triggers relatively mild, local inflammatory responses in the host (4).

Enterobiasis can take two forms: asymptomatic and clinically manifested. Most infections with *E. vermicularis* are asymptomatic or with non-specific symptoms (upper- and lower-dyspeptic and neurasthenia-like syndromes). The main symptom of the disease is perianal itching caused by mechanical irritation of the perianal folds during the egg laying, which may damage of the epidermis and lead to secondary bacterial infections. The infected may become irritable, with poor appetite, restless night sleep and bruxism (teeth gnashing ). Abdominal discomfort, loss of appetite, weight loss, insomnia, anxiety may be observed (5,6). With significant parasitic load due to ingestion of a large number of eggs or frequent reinfections, itching becomes permanent, painful and leads to excoriations, secondary bacterial infections and dermal inflammation. Other complaints include headache, dizziness, insomnia, increased irritability and distraction, weight loss. Among the observed complications are acute appendicitis, vulvovaginitis, urethritis and cystitis (7,8). Patients with enterobiasis, especially children, are often reinfected (autoreinfection) (9), as a result of a large number of eggs present under the fingernails, on the clothing, and bedding and their high resistance in the environment where the eggs can survive for 2-3 weeks (6).

Disease diagnosis is based on anamnestic and clinical data, and the results of parasitological examination. The parasitological methods for diagnosis of enterobiasis are macroscopic (detection of pinworms in the stool and/or the perianal area) and microscopic: helminthoovoscopy of material from the perianal folds, most often perianal imprint taken with transparent scotch tape (Graham's method). The sample is sealed and the eggs retain their structure for about 6 months (3). Enterobiasis is a cosmopolitan community-acquired atypical anthroponosis. It is thought to be common in humans, but other animals, including chimpanzees, gibbons and marmosets may also be infected (10). In 1983, *Enterobius gregorii* was described among Old World primates, and later - among Korean children. However, subsequent genetic studies have shown that it was not a different species (11).

The disease caused by *Enterobius vermicularis* is most common in 5 to 14 years old children (12). In older age groups, the infection rate is lower due to the development of hygienic habits (13). Children at school, especially those engaged in group activities, have higher rates of infection (14). Human-to-human transmission is common among family members as well as among those living in various

social institutions (9). The high contagiousness of enterobiasis favors its ubiquity around the world. The incidence varies considerably among the age groups (15). The prevalence of enterobiasis in Western Europe reaches up to 30% (16). In Denmark it occurs in 29% (17), and in Poland - in 10.1% of children aged between 5 and 12(18). Crotti and D'Annibale (2006) reported *Enterobius vermicularis* infection in 13.4% of the studied children in Italy (19). Prevalence among children reaches up to 61% in some communities in India, 50% - in England, 39% - in Thailand, 37% - in Sweden, and 29% - in Denmark (6). In Bulgaria this is the most common parasitic disease (20, 21). Summarized data on parasitic diseases in Bulgaria for the period 2013-2014 indicate that the average prevalence among the tested for enterobiasis 1,056,802 persons (500,251 in 2013 and 556,554 in 2014) is 0.81% (0.75% for 2013 and 0.87% in 2014). Most affected were children between 1 and 7 years old - 1.1% (22). In 2018, a total of 437,817 people were examined, and the prevalence among them was 1.45% (6331 infected). A study that included a total of 157,307 children from different types of kindergartens established a prevalence of 2.15% (3357 infected) (21). Data for 2019 revealed the presence of *E. vermicularis* in over 1.5% of those studied (23). Although a slight decrease was documented in 2020 (1.54%), the prevalence of *E. vermicularis* among organized children's groups still remained high (2.76%) (24).

According to a study by Kang et al. (2006) the annual prevalence of enterobiasis varied regionally in Korea. They also found a gender-associated difference: 9.3% among boys and 6.3% among girls (25). A study in Slovakia among children aged 5 months -15 years, established the highest prevalence in the group 3 - 6 years (5.03%), and a higher prevalence of 4.07% among boys as compared to 3.21% among girls (26).

*Enterobius vermicularis* is one of the most ancient parasites in humans (27). Paleoparasitological studies have revealed the presence of parasite eggs in 10, 000 years old human coprolites found in North America and in coprolites from Chile and Peru dating from 2200 to 400 BC. (27). The molecular diagnostics of *E. vermicularis* based on the conserved region of 5S ribosomal RNA (rRNA) in coprolites from archaeological sites in Chile and North America allows for accurate identification and comparison of ancient parasitic sequences with those of modern populations (28).

## MOLECULAR-BASED METHOD FOR CHARACTERIZATION OF *ENTEROBIUS VERMICULARIS* IN THE HUMAN POPULATION

The main method for diagnosis of enterobiasis is the identification of parasitic eggs by microscopic ovoscopy on scotch tape (29). However, this method may be of little diagnostic value at low parasitic load (30). According to published studies, the determination of *Enterobius vermicularis*-specific DNA in a fecal sample may allow the detection of the disease (31). The available literature suggests that the molecular studies of this parasite in humans are limited and that the genetic variability and its epidemiology based on molecular typing have not been fully investigated (32). In 2008, Kang et al. determined the complete sequences of the mitochondrial genome of *E. vermicularis* (33). It consists of a 14,010-bp circular DNA molecule encoding 36 genes (12 proteins, 22 transport RNAs and 2 ribosomal RNAs). The arrangement of mitochondrial DNA genes of *E. vermicularis* is unique as compared to the other nematode species. The need for further research to determine the genetic diversity of pinworms has been noted (33), but to date only limited data are available on the nuclear DNA of *Enterobius vermicularis*.

In 2006, a phylogenetic study conducted in Japan, identified 3 different clusters (designated as types A, B and C) based on the sequencing of the gene encoding the mitochondrial subunit 1 of cytochrome oxidase (*cox*1) in *Enterobius vermicularis* samples obtained from chimpanzees and humans (11). In 2011, Piperaki et al. carried out the first study of the genotypes of *Enterobius vermicularis* in scotch samples from children in Greece. Using primers to amplify a segment of the *cox*1 gene of *Enterobius vermicularis*, 11 different haplotypes were identified, all sequences falling into a type previously characterized as type B, which so far has been reported only in chimpanzees (32). In contrast to these two studies, based on *cox*1 sequencing, a study in Germany found no variation

in the ribosomal DNA region of *E. vermicularis* (31). According to the results, molecular analyzes after amplification and sequencing of *Enterobius vermicularis* ribosomal DNA (rDNA) from mature parasites (amplification of 18S rDNA fragments) cannot be used to distinguish different isolates, but is useful only for diagnostic purposes (31). In 2013, a genetic study of *E. vermicularis* identified 22 haplotypes in 58 samples from Denmark and 5 haplotypes in 15 samples from Germany (34), and no population differences between the two geographical regions. Most of the amino acid sequences of the Danish samples (88%) were type B compliant (11) and identical to 3 of the Japanese haplotypes as well as the Greek ones (34). In 2014, Hagh et al. (2014) investigated the existence and distribution of different genotypes of *E. vermicularis* based on *cox*1 genes by the method of direct sequencing of parasite eggs on scotch samples from Iran. According to the results, all samples belonged to cluster B, and the phylogenetic analysis etablished 2 subtypes: B1 and B2. All sequences identified as B1 subtype were different as compared to the other sequences in GenBank, while B2 sequences were similar to the isolates from Denmark and Greece. The results of the phylogenetic analysis of *E. vermicularis* revealed that all isolates belonged to 2 haplotypes and the studied population was likely infected from a common source (35). The molecular characterization of *E. vermicularis* in samples from Polish children using DNA from adult female parasites and primers targeting the *cox*1 gene region found that all sequences belonged to type B cluster, with isolates derived from humans from Denmark, Germany, Greece and Japan. According to these authors, type B is the only genetic type of the parasite identified in Europe (18). Phylogenetic analysis of *E. vermicularis* isolates obtained from children in Thailand based on *cox*1 gene sequences showed 66 haplotypes, grouped in 11 clusters (type A and B): 6 haplotypes fell into type A (identical to the sequences from Japan and Korea), and 5 were type B (identical with sequences from Japan, Iran, the Czech Republic, Greece, Denmark and Sudan). The authors suggested that transmission of type B haplotype parasites from primates to humans in Asia or from humans in Europe likely occurred in Thailand (36).

According to literature data, the populations of *E. vermicularis* from different countries differ significantly (34). Data on common genotypes are limited and contradictory. Analysis of mitochondrial *cox*1 gene sequences in isolates of this parasite from humans and chimpanzees revealed the presence of three different genetic species, designated as types A, B and C (11). Type B is thought to be the predominant type in humans, but additional genetic analysis of samples from different geographical locations is needed to clarify these results.

## IMPACT OF *E. VERMICULARIS* ON THE LOCAL IMMUNITY OF THE INTESTINAL MUCOSA IN INFECTED INDIVIDUALS

Data suggests that the main immune response to helminthic invasions is Th2-type, associated with an increase of eosinophils, mast cells, basophils, IgE, IL-4 and other Th2 cytokines, including IL-5 and IL-13 (37). Studies in Greek children have shown a Th2-type oriented immune response in enterobiasis, with elevated levels of serum IgE and eosinophilic cationic protein (ECP) (38). Infection with *Enterobius vermicularis* in children leads to suppression of nonspecific immunity and secondary immunodeficiency, decrease the production of hydrochloric acid and reduce the bactericidal action of the gastric juice which may lead to dysbacteriosis. Co-invasions with other parasites are not uncommon (26). Immunological activity in the gastrointestinal tract can be determined using secretory IgA (sIgA). Fecal sIgA antibodies are produced by mucosal tissues and are the major defense mechanism of the gastrointestinal mucosa (39). They play a key role for the normal function of the gastrointestinal tract by binding to antigenic epitopes of invading microorganisms, limiting their motility and adhesion to mucous membranes (40), preventing the passage of antigens into the systemic circulation and bringing to their direct excretion with the feces. Lack of sIgA causes various inflammatory diseases (41). Studies have shown that enterobiasis is associated with a significant decrease in intestinal sIgA levels (42), which increase after treatment. Analysis of the available information reveals that helminth infections lead to imbalance in the intestinal microflora (43). The symptoms and syndromes of intestinal parasitic disease are

extremely varied and not always pathognomonic. The microscopic detection in feces of parasites, especially helminths, which cause asymptomatic or mild forms of the disease, is not always associated with gastrointestinal symptoms. In these cases, a correct diagnosis requires the exclusion of other intestinal agents (44). Studies by Lee et al. (2014) showed that individuals infected with helminths (*Trichuris spp*. and *Ascaris spp.*) have elevated levels of *Paraprevotellaceae*, *Mollicutes*, *Bacteroidales*, and *Alphaproteobacteria*, and those who are not infected with these parasites have elevated levels of *Bifidobacterium* (43). Research by Yang et al. (2017) for the influence of *Enterobius vermicularis* on the intestinal microbiome indicates the presence of the following bacterial phyla: *Bacteroidetes*, *Firmicutes*, *Proteobacteria*, *Actinobacteria*, *Verrucobacteria* and *Fusobacteria*. Enterobiasis is associated with an increase in *Faecalibacterium prausnitzii*, *Ruminococcus flavefaciens*, *Alistipes purtredinis*, *Bifidobacterium longum* and *Oscillospira spp*., and with a decrease in the amounts of *Acidaminococcus intestine*, *Megasphaera elsduslai*, *Veillonella dispar*. According to the results of Yang et al. *Enterobius vermicularis* infection and mebendazole treatment were associated with changes in the intestinal microbiome (42).Studies on concomitant intestinal microflora in helminth-infected individuals have been limited and performed mostly on animal models (45). Analysis of the influence of *E. vermicularis* on the local immunity, evaluated by the levels of sIgA antibodies and the presence of pathogenic intestinal flora in *Enterobius vermicularis*-infected individuals in Bulgaria has not been performed. Such data will supplement the information on the clinical course of the disease and will help to define its accompanying pathological events.

## CONCLUSION

Human enterobiasis is a parasitic disease of medical and social importance in Bulgaria, due to its wide distribution among different age groups of the population. The survey of parasitic diseases in Bulgaria showed a significant increase in the incidence of *E. vermicularis* infection in the recent years, which requires improved measures for its control. The development of appropriate genetic methods for identification of the parasite will improve diagnosis, and the phylogenetic determination by sequencing will provide information about the common genotypes in the country. Research on the local intestinal immunity including sIgA antibodies and pathogenic intestinal bacterial flora in patients with enterobiasis would be useful to improve the quality of diagnosis and monitoring of the disease.

## ACKNOWLEDGMENTS

This work is supported by the Bulgarian National Science Fund (project no. KP-06-H53/4/11.11.2021) under the "Competition for financial support for basic research projects –2021".

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