

Opisthorchiasis in the Russian Federation: An urgent public health problem

Rusya Federasyonu'nda opisthorchiasis: Acil bir halk sağlığı sorunu

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ABSTRACT

This review is to establish the role of opisthorchiasis in health care in the Russian Federation and assess the relevance of histological and histochemical methods in determining the effectiveness of drugs against genus *Opisthorchis* helminthes - causative agents of opisthorchiasis. The analysis of literature sources, and scientific articles on the study of opisthorchiasis, the spread of its pathogen and its significance for public health have been carried out. In 2018, more than 19 thousand cases of opisthorchiasis were registered in the Russian Federation (an indicator of 12.99 per 100 thousand of the population), which made up 79.5 % of all registered biohelminthiasis in the population. The disease of opisthorchiasis is characterized by a long course, proceeds with frequent exacerbations. The most serious complication is the cancer of the liver, bile ducts, and pancreas. The works of many authors reveal the connection and high incidence of cholangiocarcinoma with the incidence of opisthorchiasis in countries with endemic foci of invasion of representatives of the Opisthorchiidae family. Long-term opisthorchiasis invasion reduces the effectiveness of anthelmintic therapy and leads to the appearance of recurrent forms of the disease. *Opisthorchis viverrini* was officially recognized as a group one biological carcinogen by the International Agency for Research on

ÖZET

Bu derlemede, Rusya Federasyonu'ndaki sağlık hizmetlerinde opisthorchiasis'in rolü ortaya konulmuş ve opisthorchiasis'in etkeni olan *Opisthorchis* helmintlerine karşı ilaçların etkinliğini belirlemede histolojik ve histokimyasal yöntemlerin uygunluğu değerlendirilmiştir. Bu Opisthorchiasis çalışmasında, patojenin yayılması ve halk sağlığı için önemi hakkındaki bilimsel makalelerin analizi yapılmıştır. 2018 yılında, Rusya Federasyonu'nda 19 binden fazla opisthorchiasis vakası kaydedilmiştir (nüfusun 100 binde 12.99'u), bu da nüfusta kayıtlı tüm biyohelmintiyazların %79,5'ini oluşturmaktadır. Opisthorchiasis hastalığı uzun bir seyir ile karakterizedir, sık alevlenmelerle ilerler. En ciddi komplikasyon karaciğer, safra kanalları ve pankreas kanseridir. Birçok yazarın çalışmaları, Opisthorchiidae ailesinin temsilcilerinin istilasının endemik odakları olan ülkelerde opisthorchiasis insidansı ile kolanjiokarsinomun yüksek insidansını ve bağlantısını ortaya koymaktadır. Uzun süreli opisthorchiasis istilası, antelmintik tedavinin etkinliğini azaltır ve hastalığın tekrarlayan formlarının ortaya çıkmasına neden olur. *Opisthorchis viverrini*, 2009 yılında Uluslararası Kanser Araştırmaları Ajansı tarafından birinci grup biyolojik kanserojen olarak resmen kabul edilmiştir. *Opisthorchis felineus* Linnaeus

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Cancer in 2009. The carcinogenic role of *Opisthorchis felineus* Linnaeus 1758 (Platyhelminthes, Cestodes, Opisthorchiidae) is not well understood. However, the life cycles, morphology, localization in the human body of *O. viverrini* and *O. felineus* are similar. In the list of studied drugs with opisthorchocidal action, special attention, and interest are paid to herbal products. Histological and histochemical methods of research confirmed the effectiveness of such herbal preparations as Ecosol, Erlim and Artemisin against *Opisthorchis felineus*.

Key Words: Opisthorchiidae, opisthorchiasis, herbal preparations, cholangiocarcinoma, zoonosis, human health, Russia

1758'in (Platyhelminthes, Cestodes, Opisthorchiidae) kanserojen rolü iyi anlaşılmamıştır. Ancak *O. viverrini* ve *O. felineus*'un yaşam döngüleri, morfolojisi, insan vücudundaki lokalizasyonu benzerdir. Opisthorchocidal etkisi olan ilaçlar listesinde, bitkisel ürünlere özel dikkat ve ilgi gösterilmektedir. Histolojik ve histokimyasal araştırma yöntemleri, Ecosol, Erlim ve Artemisin gibi bitkisel preparatların *Opisthorchis felineus*'a karşı etkinliğini doğrulamıştır.

Anahtar Kelimeler: Opisthorchiidae, opisthorchiasis, bitkisel preparatlar, kolanjiokarsinom, zoonoz, insan sağlığı, Rusya

INTRODUCTION

Foodborne parasites are a source of human parasitic infection. Zoonotic infections of humans arise from a variety of domestic and wild animals, including sheep, goats, cattle, camels, horses, pigs, boars, bears, felines, canids, amphibians, reptiles, poultry, and aquatic animals such as fishes and shrimp (1-4). Opisthorchiasis, from the group of biohelminthiasis, causes considerable damage to the health of the population (5-8). Most of the global area of opisthorchiasis is located on the territory of Russia (9, 10), the boundaries of which are expanding and, therefore, opisthorchiasis remains an urgent socially significant health problem, consistently occupying the 4th - 5th place among parasitic diseases annually (6). The significance of this trematodosis and its complications is determined by the fact that the long course of the disease, rapid in the rate and mass involvement of new contingents of the population in the process, significantly reduce the activity and life potential of the infested. The course of the disease in this nosology is often accompanied by chronicity of the process and irreversible complications, and in

some cases, it is fatal (11).

Opisthorchis viverrini Walb 1758 and *Opisthorchis felineus* Linnaeus, 1758 (Platyhelminthes, Cestodes, Opisthorchiidae) have long been recognized as the cause of serious problems with human health (12, 13). *Opisthorchis viverrini* is an endemic helminthiasis in Southeast Asia and a major public health problem in Thailand, Laos, Vietnam, and Cambodia (14, 15). Eight million people in Thailand and two million people in the Laos Democratic Republic have been estimated to be infected with *O. viverrini* (15). The population of these countries become infected with the causative agent of the disease as a result of eating fish containing larvae - metacercariae. In Thailand, this helminth affects 80% of the population. In the Russian Federation, Ukraine and Kazakhstan, the causative agent of the disease is mainly *Opisthorchis felineus*, which is confined to river systems (9, 16). According to our hypothesis, an increase in the flow of immigrants, the development of tourist travel and an increase in the import of fishery products contribute to the expansion of the boundaries of these helminthiasis.

Infection with the causative agent of opisthorchiasis occurs when eating raw or insufficiently heat-treated infected river fish containing metacercariae of trematodes (17). The main source of *Opisthorchis* spp. eggs is domestic carnivores and omnivores (cats, dogs, and pigs), especially cats and dogs. Cats are considered a good indicator of the opisthorchiasis situation in different territories. Wild animals play an additional role (mink, sable, fox, ferret, wolf, water rat, beavers, muskrat, and bear) (18).

There are several endemic foci of opisthorchiasis morbidity in the Russian Federation. Almost all territories adjacent to the basins of rivers (Ob, Irtysh, Tom) and their tributaries. The basin of the rivers Ob and Irtysh is considered to be a large, tense, the most extensive and intense world focus of opisthorchiasis (19-21). The largest foci of opisthorchiasis morbidity are located in the Khanty-Mansiysk and Yamalo-Nenets Autonomous Okrug, as well as in the Tyumen, Tomsk, Omsk and Novosibirsk regions (22, 23). The reason for this spread lies in the presence of an extremely developed river floodplain, which provides conditions for the circulation of the pathogen and a number of other factors.

The study is devoted to the analysis of literary sources on the establishment of the role of opisthorchiasis in health care and the assessment of the relevance of histological methods in determining the effectiveness of drugs against helminths - the causative agents of opisthorchiasis. The official documentation of the annual reports presented on the official websites has been studied. Moreover, our filed studies and clinical determination of opisthorchiasis in the Russian Federation in relation to histological and histochemical methods of research confirmed the effectiveness of some herbal preparations.

EPIDEMIOLOGY OF OPISTHORCHIASIS IN THE RUSSIAN FEDERATION

According to the State report "On the state of sanitary and epidemiological well-being of the population in the Russian Federation", opisthorchiasis is consistently the leading biohelminthiasis,

remaining an urgent socially significant problem of the country's health (21). In 2018, more than 19 thousand cases of opisthorchiasis were registered in the country (indicator 12.99 per 100 thousand population), which was 79.5 % of the number of all registered biohelminthiasis among the population in 2018 (Fig. 1). When compared with 2017, more than 18.7 thousand cases were registered (12.79 per 100 thousand of the population); there is an increase in the disease of the population with opisthorchiasis in the country. However, the true number of patients with helminthiasis always significantly exceeds the data of official statistics. The high incidence of opisthorchiasis among the population is aggravated by social factors: an increase in the diet of the population of coastal towns and villages in the amount of fish and home-cooked fish products (it is not possible to overcome the habits of the local population to eat raw fish); an increase in the number of amateur fishermen. According to laboratory studies, the proportion of detection of helminth larvae in fish in 2018 was 0.77 % and, when compared with previous years, the indicator is decreasing (Fig. 1) (in 2017 - 1.07 %, in 2016 - 1.26 %, in 2012 - 2.7 %, in 2008 - 2.8 %) (24).

The disease of opisthorchiasis is characterized by a long course, proceeds with frequent exacerbations. Chronic opisthorchiasis with a long course of the disease is accompanied by the development of a number of serious complications that require surgical treatment. The most serious complication is the cancer of the liver, bile ducts and pancreas (13, 25). Morphologically, up to 80 % of tumors are cholangiocarcinomas (26). The works of many authors reveal the connection and high incidence of cholangiocarcinoma with the incidence of opisthorchiasis in countries with endemic foci of *Opisthorchis viverrini* invasion (7, 27-30). This is confirmed by international epidemiological studies, according to which in the northern regions of Thailand, which are endemic foci of *O. viverrini* invasion, the incidence of cholangiocarcinoma reaches 96 cases per 100 thousand. Cholangiocarcinoma is considered

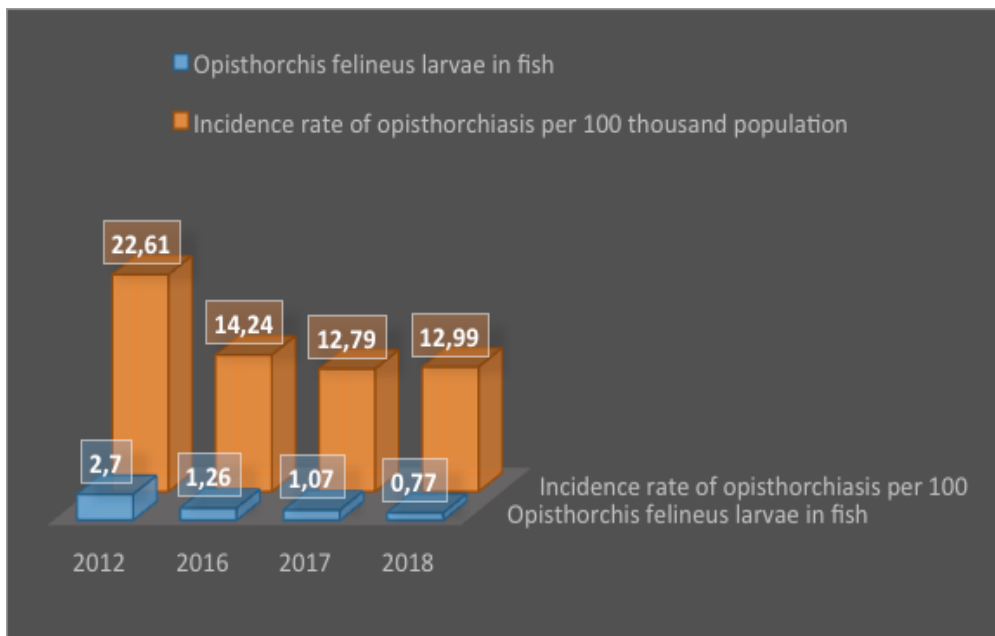


Figure 1. The proportion of detection of *Opisthorchis felineus* larvae in fish and the incidence rate of opisthorchiasis per 100 thousand populations in the Russian Federation (24).

a fatal tumor and is common in endemic areas where the causative agent of opisthorchiasis is present (31). The occurrence of primary liver cancer correlates with the duration and intensity of opisthorchiasis invasion. Prolonged and especially massive parasitic invasion is accompanied by pronounced dystrophic and necrotic changes in the walls of the biliary and pancreatic systems with pathological intensive regeneration of the epithelium and the formation of adenomatous growths, metaplasia of the epithelium up to cellular and tissue atypism. Cancer can develop 30 - 40 years after infection, and death occurs 3 - 6 months after diagnosis (5). Long-term opisthorchiasis invasion reduces the effectiveness of anthelmintic therapy and leads to the appearance of recurrent forms of the disease. Reinvasions and superinvasions constantly cause additional foci of proliferation and increase the risk of malignant degeneration of the bile duct epithelium. *O. viverrini* was officially recognized as a group one biological carcinogen by the International Agency for Research on Cancer (IARC)

since 1994 (32). The carcinogenic role of *O. felineus* is still insufficiently understood (33). However, the life cycles, morphology, and localization in the human body of *O. viverrini* and *O. felineus* are similar. The mechanisms of induction of carcinogenesis by hepatic flukes have been established.

There are three ways of initiation of carcinogenesis by chronic invasion of Opisthorchis:

1. Immunoinflammatory pathway: in which an inflammatory immune response of the host organism develops in response to *Opisthorchis* antigens (34, 35). Chronic inflammation is characterized by prolonged stimulation of the cells of the immune system, a change in the profile of the cytokines they produce, as well as the migration of activated macrophages and polymorphonuclear leukocytes to the inflammation focus, which produce reactive oxygen species, proteolytic enzymes, and growth factors. The presence of these products in the focus of inflammation leads to the development of cholangiocarcinoma (36).

2. A mechanical pathway: Due to the influence of flukes during feeding and movement, which disrupts the integrity of cholangiocytes and contributes to the maintenance of chronic inflammation. The adults of *Opisthorchis* spp. mechanically interfere with the normal outflow of bile, stagnant components, which interact with each other, as well as with reactive oxygen species in the inflammation focus, form endogenous carcinogens that have a mutagenic effect on cholangiocyte DNA (37-39).

3. The impact of secretory and excretory products of *Opisthorchis* on epithelial cells of the bile ducts: Adults of *Opisthorchis* spp. being near the epithelium of the bile ducts produce low molecular weight metabolic products that interact with the components of bile or with reactive oxygen species, penetrating through the membranes of cells of the epithelium of the bile ducts, have a toxic and carcinogenic effect on the owner. In the process of their vital activity, *Opisthorchis* spp. secrete many protein products (40). They can contribute to the creation of an oncogenic environment in the body, stimulating the proliferation of host cells, preventing apoptosis, causing hyperplasia and metaplasia of the epithelium of the bile ducts, contributing to the occurrence of cholangiocarcinoma (41, 42). However, the final mechanism of carcinogenesis in opisthorchiasis has not been studied.

At present, Praziquantel (Biltricid) is considered to be the only drug providing effective chemotherapy for opisthorchiasis (35). The effective action of Praziquantel on the *Opisthorchis* organism and their egg production has been confirmed by micromorphological and histochemical studies (6). Histological and histochemical methods make it possible to study in detail the micromorphology and change metabolism in the body of helminths exposed to the drug. These methods make it possible to evaluate the effect of the drug, to identify the ways of its penetration into the body of the parasite and to reveal the mechanism, providing an informative picture and confirming the possibility of its effectiveness against the causative

agent of the disease. The morphofunctional changes in organs and tissues of *Opisthorchis felineus* after the action of drugs from different chemical groups have been studied in sufficient detail (6, 43). The micromorphological picture of the organs and tissues of *Opisthorchis* was studied after the action of Chloxyl, Bitin-S, Meniclofolan, Hetolin, Mebendazole, Albendazole, Flubendazole, Mebendazole, Praziquantel, Azinox, Medamine, Biltricide. The authors, who studied the ways of penetration of drugs into the body of *Opisthorchis*, noted strong changes after the action of anthelmintics in the tegument, parenchyma, intestines and muscles of the suckers of the parasites. Histochemically, revealed a decrease in glycogen in the tissues of trematodes, the redistribution of proteins and fats. There are works to identify the effect of drugs on the body of *Opisthorchis viverrini* (44).

In the list of studied drugs with against *Opisthorchis*, special attention and interest is paid to herbal remedies, since when considering the activity of anthelmintics, the attention of researchers is directed not only to their helminthic action, but also to reduce toxicity (45). Herbal preparations have historically been the first remedies for the treatment of helminthiasis; their composition does not allow parasites to adapt to them (46). Many anthelmintic herbal preparations can be used for a long time (from 2-3 months to a year) without harming the body of the host, which cannot be said about synthetic agents. Histological and histochemical research methods have confirmed the effectiveness of such herbal preparations as Ecosol, Erlim and Artemisin against *Opisthorchis felineus* (24, 47).

Despite the significant advances achieved on theoretical and practical issues of human disease with opisthorchiasis and its causative agent, the tense epidemiological situation of the population for diseases caused by representatives of Opisthorchiidae, their carcinogenic effect on the human body emphasizes the importance of preventing opisthorchiasis, the need for its timely detection, treatment and requires further

research. In this regard, histological, histochemical and morphometric studies of tissues and organs of trematodes remain relevant and helping to elucidate the mechanism of action of anthelmintics allowing to establish the degree of structural disorders and predict their “reversibility “ or “ irreversibility “.

CONCLUSION

Analysis of literature sources showed that the epidemiological situation of the population for opisthorchiasis is tense and opisthorchiasis remains a serious health problem, not only in Russian

Federation, but also in the world. Representatives of Opisthorchiidae parasitizing in the hepatobiliary tract of the host, producing toxic and immunogenic waste products, disrupting cell metabolism, and are one of the factors contributing to the development of bile duct cancer. Histological and histochemical research methods used to study changes in the body of trematodes (*Opisthorchis*) that occur after the action of anthelmintic drugs are informative and allow you to establish the degree of effectiveness of the drug.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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