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CHARACTERISTICS AND OCCURRENCE OF CORONAVIRUSES
IN HUMANS AND ANIMALS

CHARAKTERYSTYKA ORAZ WYSTĘPOWANIE KORONAWIRUSÓW
U LUDZI I ZWIERZĄT

Marcin Weiner^{1(A,B,C,D,E,F,G,H)}, Karolina Tarasiuk^{2(A,B,C,D,E,F)}

¹Faculty of Health Sciences, Pope John Paul II State School of Higher Education in Biała Podlaska, Poland

²The Provincial Specialist Hospital in Biała Podlaska, Poland

Authors' contribution

Wkład autorów:

- A. Study design/planning
zaplanowanie badań
- B. Data collection/entry
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- C. Data analysis/statistics
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Summary

Coronaviruses occurring in humans and animals are a diverse group of pathogens, characterized by high variability and tropism. The most serious animal diseases caused by coronaviruses include equine coronavirus disease (E-CoV), canine coronavirus disease (C-CoV), rabbit enteric coronavirus disease (Rb-CoV), infectious bronchitis in poultry (IB-CoV), epizootic catarrhal enteritis in ferrets, in pigs: transmissible gastroenteritis coronavirus disease (TGE), human enteric coronavirus disease (HE-CoV), and porcine epidemic diarrhea (PED), in cattle (Bo-CoV): neonatal calf diarrhea, respiratory tract infections, winter dysentery in cattle, in cats: feline enteric coronavirus disease (FE-CoV) and feline infectious peritonitis (FIP-CoV). To date, three major epidemics causing severe respiratory diseases in humans (SARS-CoV-1, MERS-CoV, SARS-CoV-2) have been reported. Due to the high morbidity and mortality rate, coronavirus-induced diseases in animals result in serious economic losses. The current human COVID-19 pandemic demonstrates the need for action to modernize and improve diagnostics in this area, but also to develop innovative immunoprophylactic and therapeutic methods.

Keywords: coronaviruses, pandemic, COVID-19, SARS, MERS

Streszczenie

Koronawirusy występujące u ludzi i zwierząt są bardzo zróżnicowaną grupą patogenów, charakteryzujących się dużą zmiennością i tropizmem. Do najgroźniejszych chorób zwierzęcych, wywoływanych przez koronawirusy, zalicza się koronawirusę koni (E-CoV), koronawirusę psów (C-CoV), koronawirusę przewodu pokarmowego królików (Rb-CoV), zakaźne zapalenie oskrzeli u kur (IB-CoV), epizootyczne nieżytowe zapalenie jelit u frettek, u świń: koronawirusowe zapalenie żołądka i jelit (TGE), chorobę wymiotną i wyniszczającą (HE-CoV), a także epidemiczną biegunkę (PED), u bydła (Bo-CoV): biegunki nowonarodzonych cieląt, nieżyt dróg oddechowych, zimową dyzenterię bydła mlecznego, u kotów: koronawirusowe zapalenie jelit (FE-CoV) i zakaźne zapalenie otrzewnej (FIP-CoV). Do chwili obecnej odnotowano trzy wielkie epidemie powodujące u ludzi ciężkie choroby układu oddechowego (SARS-CoV-1, MERS-CoV, SARS-CoV-2). Z uwagi na wysoki współczynnik zachorowalności i śmiertelności, choroby wywoływane przez koronawirusy u zwierząt prowadzą do poważnych strat na tle gospodarczym. Obecna pandemia COVID-19 u ludzi wskazuje na konieczność podjęcia działań zmierzających do zmodernizowania i udoskonalenia diagnostyki w tym zakresie, ale również do opracowania innowacyjnych metod immunoprophylaktycznych i leczniczych.

Słowa kluczowe: koronawirusy, pandemia, COVID-19, SARS, MERS

Introduction

Characteristics of coronaviruses in humans and animals

Coronaviruses are a very interesting and diverse group of pathogens, capable of infecting not only humans but also animals. They can cause a wide range of diseases affecting the respiratory, excretory, digestive, and even nervous systems. Coronaviruses belong to the order *Nidovirales*, the suborder *Cornidovirineae*,

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Address for correspondence / Adres korespondencyjny: Marcin Weiner, Faculty of Health Sciences, Pope John Paul II State School of Higher Education, Siderska 95/97, 21-500 Biała Podlaska, Poland, e-mail: m.weiner@pswbp.pl, phone: +48 83 344 99 00
ORCID: Marcin Weiner <https://orcid.org/0000-0001-9288-0823>, Karolina Tarasiuk <https://orcid.org/0000-0002-5926-5121>

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Coronaviridae family, *Orthocoronavirinae* subfamily. There are four types of coronavirus, identified by genetic differences in their structure: *Alphacoronavirus* and *Betacoronavirus* (capable of infecting mammals only) as well as *Gammacoronavirus* and *Deltacoronavirus* (capable of infecting birds, but also certain mammals) [1]. The aim of this work is to present the latest information regarding the characteristics of coronaviruses occurring in humans and animals.

Due to their high infectivity and mortality rate, their ability to cause epidemics, as well as the severity of the diseases they cause, coronaviruses induce fear in people and disorganize society. Over a period of two decades, three major Betacoronavirus epidemics have been reported in humans: SARS and COVID-19 (severe acute respiratory syndrome) and MERS (Middle East respiratory syndrome).

The SARS epidemic took place in 2002-2003 and was caused by the SARS-CoV-1 virus. It was brought under control in less than a year, but as a result of the epidemic more than 8,000 people were infected. The mortality rate of the virus was 9.5% [2].

The COVID-19 epidemic began in 2019 in China as a result of the spread of SARS-CoV-2 and continues to this day. To date, 8.8 million people worldwide have been infected, of whom 4.37 million have recovered and 465 thousand have died [3].

The final coronavirus epidemic – MERS-CoV – began in 2012 and, as with COVID-19, continues to this day. By the end of 2019, almost 2.5 thousand people had been infected. The mortality rate was 42% [4].

The coronaviruses responsible for these outbreaks are believed to have originated from bats as the primary reservoir, while other animals have acted as intermediate hosts, allowing them to spread to humans and other animals. The intermediary in the spread of the virus from the natural reservoir to humans, in the case of SARS-CoV-1 virus, was the masked palm civet [5], in the case of MERS-CoV virus – these are one-humped camels (dromedaries) [6], while in the case of SARS-CoV-2 virus – probably the sunda pangolin [7].

The most serious animal diseases caused by coronaviruses include:

- equine coronavirus disease (E-CoV) [8],
- canine coronavirus disease (C-CoV) [9],
- rabbit enteric coronavirus disease (Rb-CoV) [10],
- infectious bronchitis in poultry (IB-CoV) [11],
- epizootic catarrhal enteritis in ferrets [10],
- in pigs: transmissible gastroenteritis coronavirus disease (TGE), human enteric coronavirus disease (HE-CoV), and porcine epidemic diarrhea (PED),
- in cattle (Bo-CoV): neonatal calf diarrhea, respiratory tract infections, winter dysentery in cattle [12],
- in cats: feline enteric coronavirus disease (FE-CoV) [13] and feline infectious peritonitis (FIP-CoV) [14].

Coronaviruses are enveloped viruses with a size ranging from 120 to 160 nm. Their genome is made up of positive-strand RNA up to 32 kb in size, which makes it one of the largest genomes among the RNA viruses [15]. The name 'coronavirus' derives from the characteristic appearance of the virus, which resembles a crown which is formed around the virus by a protein envelope with club-shaped spikes. In addition to the club-shaped spikes made of protein S, it also has other structural proteins – a matrix protein M and a small envelope protein E. Additional structural proteins may be present (as in the case of SARS-CoV-1) – hemagglutinin-esterase (HE). Furthermore, inside the virion there is a nucleoprotein N which assembles into nucleocapsid. Two thirds of the genome are responsible for encoding the viral replicase, while the rest is responsible for encoding structural and accessory proteins. To date, the knowledge about the function of accessory proteins in coronaviruses is not fully understood; however, it is believed that they may be responsible for their pathogenicity [16].

A fundamental role in the initial phase of infection is undoubtedly played by the S-protein, which enables the virus to penetrate the host cells, with the use of different receptors depending on the species. In the case of SARS-CoV-1 or SARS-CoV-2, they are likely to recognize ACE2 (angiotensin-converting enzyme 2) receptors located on the surface of the alveoli. ACE2 receptors may have structural differences and exist in different variants, which may explain the variable level of human susceptibility to infection [17].

Among important bodily defenses against infection is the apoptosis of infected cells, inhibiting the replication of the virus. Viruses can evade it by encoding proteins homologous to the mammalian Bcl-2 family proteins that regulate apoptosis. Induction of apoptosis by viruses in the immune system creates suitable conditions for the spread of infection and development of the disease [18]. As a result of the interaction between the coronavirus and the infected organism, the behavior of the immune system changes, which translates into the initiation of an immune response or its avoidance. In the case of human coronavirus infections, suppression of interferon synthesis takes place, which probably results from the shielding of the coronavirus RNA with double membrane vesicles. This, in turn, prevents contact with pattern-recognizing receptors (PRRs) [19].

Coronaviruses have a characteristic feature of genetic variability, which determines their biological properties

(e.g. pathogenicity, tropism, and host adaptation), which in some cases may cause the occurrence of infectious diseases of unknown characteristics [6]. Genetic changes are possible due to three different mechanisms:

- mutations, or a greater number of, particular nucleotides, resulting in local changes in the RNA,
- recombination, i.e. the exchange of specific genome elements between viruses which gives rise to viruses that have different genetic information from their original strains,
- the acquisition and loss of genes, which primarily concern coronaviruses infecting humans in relation to accessory proteins, which results in a complete change in the viral phenotype, and determines changes in tropism, virulence and the ability to evade immune system responses [20].

Human coronaviruses

In 1966, the coronavirus HCoV-229E was first recognized in humans, the reservoir of which was a bat. So far, seven coronaviruses capable of infecting humans have been identified:

- four of them – HCoV-229E, HCoV-HK1, HCoV-NL63 and HCoV-OC43 – cause, among other things, colds and bronchitis and pneumonia [21],
- the other three – SARS-CoV-1, MERS-CoV, SARS-CoV-2 – cause severe respiratory distress.

The COVID-19 pandemic was caused by the SARS-CoV-2 virus in late 2019. The incubation period ranges from 2 days to 2 weeks (about 5-6 days on average). In most cases, the disease has a mild course. Its characteristic symptoms are high temperature (above 38°C), coughing, shallow breathing, or shortness of breath, as well as flu-like ailments – sneezing, rhinitis, sore throat. Intestinal complaints are rare. In severe cases of COVID-19, pneumonia leading to acute respiratory distress (ARDS) and sepsis, and in extreme cases – septic shock and death [22].

There are three forms of the disease:

- mild, involving only the upper respiratory tract,
- non-life-threatening pneumonia,
- acute pneumonia with ARDS, which develops approximately 7 days after infection.

The coronavirus SARS-CoV-2 was first identified in 47 women from Wuhan (China). RT-PCR laboratory tests carried out on the fourth, fifth and sixth days of infection confirmed its presence in smears taken from the throat, saliva, and feces. Seven days after infection, no coronavirus was found in the patient, however, there was an increase in specific IgM/IgG antibodies in the blood, which persisted for 7 days after COVID-19 symptoms had completely disappeared [23].

The coronavirus SARS-CoV-1 was identified in 2003 in Gudang-Dong (China). The characteristic symptoms of the disease are cough and fever leading to atypical pneumonia, which in severe cases develops into ARDS with high mortality [24]. The virus is transmitted through small droplets. Bats are its natural reservoir, but civets act as indirect hosts in the spread of the virus to humans. It is believed that the inter-species barrier between bats and humans is likely to have been crossed because bats are considered to be the host of most known coronaviruses [25].

The MERS-CoV coronavirus was first diagnosed in 2012 in Saudi Arabia, where the highest number of infections was reported (over 2 thousand) [26]. As a result of the epidemic caused by the virus, 780 people died [27]. The most common symptoms of MERS-CoV infection are flu-like symptoms – sneezing, coughing, elevated body temperature. This is accompanied by dyspnea. The clinical course of acute infection is characterized by pneumonia leading to ARDS syndrome and/or internal organ (particularly kidney) dysfunction, which is itself a direct life-threatening condition that can lead to the patient's death. Bats are likely to be the reservoir of infection, whereas dromedaries, similarly to SARS-CoV-1, can act as intermediate hosts to human infection [28].

To date, no protective vaccine against coronaviruses has been invented. Infection prevention includes primarily isolating and avoiding contact with patients and those suspected of being infected as well as covering the mouth and nose when sneezing and/or coughing.

Animal coronaviruses

Bats

Bats are considered the primary, natural reservoir of coronaviruses, performing a very important function in the evolution of these pathogens. In the last decade, based on research in 20 countries, 500 new coronaviruses have been discovered in bats. Interestingly, a coronavirus identified in 2013 in Yunnan Province (China) is likely to be a potential ancestor of the COVID-19 inducing virus, given that the nucleotide sequences of its genome are

over 96% identical [29]. According to the data available in the literature, coronavirus infection has been found in 11 out of 18 groups of bat families (particularly insectivorous families). The presence of alpha coronaviruses has been reported in some European countries, on the American continent, Australia, Asia and Africa, while the presence of beta coronaviruses has been found in Latin America (Mexico), Africa (Kenya, Madagascar and the southern region of the continent), Asia (Thailand, China, Philippines), the Middle East and the European continent (Italy, Finland) [30]. Bats caused the spread of both the SARS virus in China and MERS-CoV in the Middle East, thus starting global epidemics in 2002 and 2012 [5,31].

Dogs

Dogs contract coronaviruses that cause gastroenteritis (intestinal form), respiratory symptoms (respiratory form) and multi-organ infection (systemic form). The intestinal form of coronavirus infection (C-CoV) is usually mild and self-healing [32]. The infection starts in the duodenum, then spreads through the gastrointestinal tract. The spleen and liver may also be infected. Pups are the most susceptible to this type of infection and suffer a high mortality rate. Characteristic symptoms of the infection are sudden diarrhea, weakness, and lack of appetite. The feces have the consistency of an orange-colored liquid, with an admixture of mucus and blood. Dehydration and general weakness may result in circulatory disorders [33]. Respiratory coronavirus infection (CR-CoV), is spread via small droplets, through contact with infected food, bedding, or through contact with a person who may be an intermediary host of the virus. Unless coexisting diseases are present, the infection is in the upper respiratory tract, but the possibility of pneumonia is not excluded. Mild infections resolve by themselves. The characteristic symptoms of the respiratory form are coughing, a high temperature, sneezing, nasal discharge, general malaise [34]. In extreme cases, pneumonia may occur. Reinfection results in immunity or mitigates the course of infection [35]. The systemic form of coronavirus infection, induced by a highly virulent pantropic strain belonging to subtype IIa, is characterized by high fever, depression, leukopenia, paresthesia, ataxia, and gastrointestinal problems. The lesions affect mainly the small intestine – there is a possibility of petechiae, enlarged spleen, atrophy of intestinal villi and degeneration and necrosis of intestinal crypt cells [34].

Cats

In cats there are two specific coronavirus infections that cause:

- gastrointestinal disorders (FECV) – particularly for kittens under 12 weeks of age [36]. It is usually accompanied by fever, lack of appetite, vomiting and diarrhea [37]. Infection in adult cats may be asymptomatic or mild. The virus can be transmitted through food, the air or through contact with an infected animal. It is present in nasal discharge, saliva, feces, and urine;
- infectious peritonitis (FIPV) – mainly affects cats between 3 months and 3 years of age, and cats over 10 years of age, due to immunosuppression, leukemia, or relocation. There are two forms of infection: exudative (accounting for up to 70% of all cases; characterized by anemia, apathy, fever, as well as weakness of the body caused by dehydration and lack of appetite) and non-exudative (most often with a chronic course, accompanied by the formation of granulomas on the internal organs and symptoms related to where they develop, e.g. in the case of kidney infections: polyuria, vomiting, weight loss) [14].

Cattle

According to the data available in the literature, bovine coronavirus (B-CoV) is prevalent worldwide. It is pathogenic not only for these animals, but also for animals from camel and deer families [38]. It can cause respiratory infections (in adults the course of the disease is most often mild, while in calves it can cause pneumonia), gastroenteritis in calves accompanied by diarrhea (up to 70% of the infected herd can have it) or winter dysentery in dairy cows (acute gastrointestinal disease with a high incidence and low mortality rate). Characteristic symptoms of respiratory infection are sneezing, lack of appetite, coughing, exudate from the nose and conjunctival sac, and inflammation of the nasal mucosa. The condition resolves after about 14 days and the animal recovers. In the case of infection of the stomach and intestines of calves, a characteristic symptom is yellowish diarrhea, sometimes with an admixture of blood, which later evolves into a watery, profuse form. Generally speaking, the younger the animal, the worse the course of the disease. Most young cattle usually recover, but untreated diarrhea can ultimately lead to cardiovascular collapse and death. In winter dysentery of dairy cows, diarrhea occurs unexpectedly and is watery or hemorrhagic. If it lasts longer than 2 days, it leads to dehydration. It is characterized by an unpleasant, fetid, and sweet odor in the enclosure where the animals are kept [39].

To date, no cure for bovine coronavirus infection has been discovered. The treatment is based on the use of broad-spectrum antibiotics. In calves the therapy is based on supportive care – a live, attenuated BCoV vaccine is recommended. The application of an inactivated vaccine in calves reduces the risk of coronavirus gastroenteritis in new-born calves [40].

Pigs

The porcine epidemic diarrhea virus (PED-CoV) belongs to the genus Alphacoronavirus. It is characterized by high infectivity and mortality rates, particularly among small piglets. It affects all age groups in pigs, however, in older animals the infection may be milder or asymptomatic. Specific symptoms of PED-CoV infection include apathy, vomiting and watery diarrhea with a greenish or yellowish color, which leads to severe dehydration. Dehydration mainly concerns small piglets in the first month after birth and may be fatal [41]. The virus is transmitted orally after ingestion of infected feed, or through the fecal-oral or airborne route. Prophylaxis includes the oral or intramuscular administration of an attenuated vaccination in sows about 2-4 weeks before parturition, to reduce the risk of small piglets dying as a result of dehydration.

The transmissible gastroenteritis virus (TGEV) belongs to the genus Alphacoronavirus and can affect all age groups of pigs. The disease caused by this micro-organism has an acute course in piglets up to 3 weeks old as well as in pregnant sows and immediately after birth. In other age groups the infection is milder. Infection occurs most often during the delivery of piglets. The virus is disseminated via the fecal-oral and inhalation routes, particularly in piglets of a single litter or animals housed in a single enclosure. A specific symptom of infection is greyish green diarrhea. The infection causes immunity to develop approximately 7 days after infection. Prophylaxis against gastrointestinal coronavirus includes the use of biosecurity measures [42].

Porcine respiratory coronavirus (PRC-CoV) also belongs to the genus Alphacoronavirus. It causes respiratory infection, which mainly affects piglets separated from sows. The infection occurs via the airborne route and during direct contact with infected animals [43]. The infection is accompanied by high fever (up to 40°C), lack of appetite, coughing and dyspnea [44].

The porcine hemagglutinating encephalomyelitis virus (HE-CoV) belongs to the genus Betacoronavirus. Pigs are the only natural reservoir of infection. Pigs are at high risk of infection in the first week after birth. Characteristic symptoms of the disease are apathy, paresthesia, and convulsions. The occurrence of motor coordination disorders and vomiting is not excluded. In the first 3 days after infection, the mortality rate may be as high as 100%. The coronavirus HE-CoV causing vomiting and wasting disease is asymptomatic in older individuals. To date, no vaccine has been developed against this virus [45].

The origin of deltacoronavirus PDCoV in pigs is unclear. Infection with this pathogen was first reported in 2007 in China. The infection usually manifests itself as diarrhea leading to dehydration, but the course of the infection is much milder than in the case of coronaviral gastroenteritis and epidemic diarrhea in piglets. The asymptomatic form of the infection mainly affects older animals. Due to the lack of a vaccine against this pathogen, prophylaxis is based on the use of biosecurity measures, and in the case of an infection, it includes symptomatic treatment [46].

Horses

Equine coronavirus (E-CoV) infection mainly occurs during the autumn-winter period when animals are kept indoors. The virus has a high incidence and low mortality rate. The pathogen is spread to horses through direct contact with an infected animal or a contaminated environment. Characteristic symptoms of infection are lack of appetite, high fever (up to 41°C), apathy, diarrhea and horse colic accompanied by neutropenia and lymphopenia. Most E-CoV infections involve adult individuals participating in shows and races. Treatment of the infection is difficult – it is based on the administration of non-steroidal anti-inflammatory drugs and fluids to prevent dehydration. Cases of infections manifesting intestinal colic require treatment in specialist clinics. To date, no drugs or vaccines against E-CoV have been invented [47].

Poultry

The virus causing infectious bronchitis in poultry (IB-CoV) is the longest known gammacoronavirus so far. The virus is characterized by a high changeability that affects the degree of pathogenicity and tropism, which leads to the multiple forms of the disease [48]. The virus is transmitted through the fecal-oral route or during direct contacts. The disease affects birds of different age and sex.

These factors, as well as virulence and serotype of the virus, determine the course of infection. In chickens, the infection is mainly manifested by a pale or pale colored comb, rattling in the throat, muscle tremors, weakness, and catarrh. The impairment of reproductive system functions, deterioration of egg quality and decrease in their production are not excluded [49]. In the renal form, infections are accompanied by weight loss, excessive thirst, and watery, white diarrhea, which leads to dehydration [38]. Prophylaxis of infections mainly involves adherence to the biosecurity measures, as the effectiveness of vaccination in this respect still raises many reservations [50]. Gammacoronaviruses also include the turkey coronavirus (T-CoV), which causes weight loss, diarrhea, and apathy in these birds. The mortality rate among young turkeys can be as high as 96% [51].

The coronavirus infections also affect other animal species causing, among others, transmissible enteritis (Rb-CoV), myocardial degeneration in rabbits, catarrhal enteritis in ferrets (ECE) or hepatitis in mice (MH-CoV). According to the available literature data, coronaviruses have also been isolated from European hedgehogs [52] and beluga whales [53].

The presence of the SARS-CoV-1 coronavirus has been found in masked palm civets, raccoon dogs and Chinese ferret-badgers [54]. Studies carried out on wild animals for their susceptibility to this pathogen showed that ferrets, rhesus macaques, hamsters, guinea pigs and rats were the most susceptible to infection [55].

In turn, after experimental studies on MERS-CoV infection in horses, sheep, and goats, it was found that only goats showed a negligible excretion of the pathogen [56].

The studies on SARS-CoV-2 in cats have so far shown that the virus has a high ability to infect them – the greatest risk of infection is in small kittens. It should be noted, however, that the studies were carried out on small groups of cats, to which a significant dose of SARS-CoV-2 was applied, which does not give grounds to draw unambiguous conclusions regarding their role in the spread of the virus to humans [57].

Conclusions

Coronaviruses in humans and animals can cause acute and chronic diseases. They are characterized by high genetic variability, which determines their biological properties (e.g. pathogenicity, tropism, and host-cell adaptation), which in some cases may cause the occurrence of infectious diseases of unknown characteristics. Animals are the natural reservoir of most coronaviruses and can play a key role as intermediary hosts in the spread of these pathogens to humans.

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