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Novel coronaviruses

Nowoodkryte koronawirusy

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Summary

Currently, there are six known groups of coronaviruses responsible for the disease occurring in humans. The coronaviruses 229E, OC43, NL63, HKU1-NH are a common cause of upper respiratory tract infections in humans. The course of infection is generally similar to influenza virus infection. These viruses are distributed around the world, but most commonly in Asia. HCoV-SARS and HCoV-MERS are currently regarded as the most dangerous of the known coronaviruses. HCoV-SARS infection was diagnosed for the first time in the province of Guangdong in the south-eastern China in 2002. The disease was the rapid, dominated by symptoms of respiratory failure and fever. Quick actions of epidemiologists prevented the spread of the virus and resulted in extinction beginning of the epidemic. In 2012, a new coronavirus was isolated known as a HCoV-MERS (Middle East Respiratory Virus). Epidemiological data indicate that the place of current spread of epidemic is Saudi Arabia. The probable source of infection are some species of bats and domesticated animals, mainly camels. The clinical course of infection is similar to that of the HCoV-SARS infection with coexisting symptoms of kidney damage. The mortality is about 50%. The virus is detected in Europe. The first reported cases of infection are among persons returning from the United Arab Emirates to France, Britain and Germany. Both the WHO and ECDC with great concern monitor the rapid spread of HCoV-MERS.

Streszczenie

Obecnie znanych jest sześć grup koronawirusów odpowiedzialnych za choroby występujące wśród ludzi. Koronawirusy 229E, OC43, NL63, HKU1-NH są częstą przyczyną zakażeń górnych dróg oddechowych wśród ludzi. Przebieg tych zakażeń jest zazwyczaj zbliżony do infekcji wirusami grypy. Wirusy te występują na całym świecie, jednak najczęściej w Azji. HCoV-SARS oraz HCoV-MERS uznawane są obecnie za najgroźniejsze spośród znanych koronawirusów. Zakażenie HCoV-SARS rozpoznano po raz pierwszy w prowincji Guangdong w południowo-wschodnich Chinach w 2002 roku. Przebieg choroby był gwałtowny, dominowały objawy niewydolności oddechowej i gorączka. Szybkie działania służb epidemiologicznych zapobiegło rozprzestrzenianiu się wirusa i spowodowało wygaszenie rozpoczynającej się epidemii. W roku 2012 wyizolowano nowego koronawirusa określanego nazwą HCoV-MERS (ang. *Middle East Respiratory Virus*). Dane epidemiologiczne wskazują, że miejscem, z którego aktualnie rozprzestrzenia się epidemia, jest Arabia Saudyjska. Prawdopodobnym źródłem zakażenia są niektóre gatunki nietoperzy i udomowionych zwierząt, głównie wielbłądów. Przebieg kliniczny zakażenia jest zbliżony do zakażenia HCoV-SARS, ale dodatkowo współistnieją objawy uszkodzenia nerek. Śmiertelność wynosi około 50%. Wirus trafił już do Europy. Pierwsze przypadki zachorowań zanotowano wśród osób powracających ze Zjednoczonych Emiratów Arabskich do Francji, Wielkiej Brytanii i Niemiec. Zarówno WHO, jak i ECDC z wielkim niepokojem monitorują szybkie rozprzestrzenianie się HCoV-MERS.

INTRODUCTION

Coronaviruses belong to *Coronaviridae* subfamily. These are large spheric RNA viruses with an envelope with bulbous protein projections resembling the colar corona. The genome is a single RNA strand

of helical symmetry. Coronaviruses are divided into four kinds depending on the structure of their protein sequence. HCoV-229E and HCoV-NL63 are classified to *Alphacoronaviruses* while HCoV-OC43, HCoV-HKU1, HCoV-SARS and HCoV-MERS – to *Betacoronaviruses*.

Pathogenic viruses of *Gammacoronaviruses* and *Deltacoronaviruses* have not been described yet (1). Coronaviruses can be found world-wide. They show tropism to epithelial cells of the air passages, particularly ciliary epithelial cells. Viral RNA replicates in the cellular nucleus, which it leaves and binds to a capsule part in the cytoplasm. Coronaviruses are cytotoxic to the cells they use as the replication site. They are frequent factor of upper respiratory and alimentary tracts infections. Mammals and birds are susceptible to the infections caused by these viruses. Coronaviruses are responsible for enteritis in pigs, cattle, and dogs and for peritonitis in cats (mainly coronavirus FIP).

Only two pathogenic for humans viruses (HCoV-229E and HCoV-OC43) have been known up to 2003. They were responsible for upper respiratory tract infections. At present, HCoV-NL63 and HCoV-HKU1, also responsible for upper and lower respiratory tract infections, have been described. Coronaviruses 229E, NL63, HKU1 and OC43 are viruses occurring world-wide. Numerous epidemiological data indicate China to be the most probable place of their origin.

Among coronaviruses, there are two specifically dangerous: HCoV-SARS, responsible for severe pneumonia and HCoV-MERS – responsible for pneumonia with coexisting kidney damage. The infection is usually severe with unfavourable prognosis.

CORONAVIRUSES OC43

There are four genotypes of HCoV-OC43 (from A to D). Unlike in case of such viruses as 229E, NL63 or HKU1, the season of the year does not influence the rate of droplet infection. These viruses are responsible for respiratory tract infections which frequently lead to pneumonia. Among patients with upper respiratory tract infections without pneumonia, dominating symptoms are fever, weakness, abdominal pain, rhinitis, and sore throat. Vabret et al., estimating the causes of upper respiratory infections in France, observed HCoV-OC43 infection in 6% of patients (2). The infections with these viruses can be the cause of severe pneumonia, specifically in small children, elderly people, and patients with decreased immunological response, including HIV patients. HCoV-OC43 can infect and multiply in the neurons causing inflammatory conditions and degenerative changes. It seems that these viruses can be responsible for certain undefined central nervous system damage in humans. Animal studies confirmed these viruses to be the cause of encephalitis and paralytic changes depending on viral external protein activity on the glutamate receptors (3). In HCoV-OC43 patients with CNS damage, the beneficial influence of these receptors antagonists was used (4).

It seems coronavirus infections occur more frequently in children than in adults. Dijkman et al. carried out the study in Amsterdam in the group of 1471 children hospitalized due to respiratory tract infections and observed in 14% of children the infection with OC43, HKU1, 229E, and NL63 coronaviruses. HCoV-OC43

infections are the most frequent infections among isolated coronaviruses (5). In the studies, carried out in Brazil by Cabeça et al., coronaviral infections were observed in 88 out of 1137 (7.7%) adult patients hospitalized due to the symptoms of respiratory tract infections. The kind of coronaviruses that are the most frequent cause of infections changes in particular years. The studies, performed by Cabeça et al. in Brazil in 2004-2008, revealed that the coronavirus responsible for infections in 62% of patients was mainly HCoV-229E while in 2008 it was HCoV-NL63 (71%) (6).

CORONAVIRUSES 229E

HCoV-229E is human pathogen with no pathogenic activity to other mammals or birds. They bind to superficial receptors of the cells built with aminopeptidases and metalloproteinases. These receptors occur most frequently on epithelial cells of the intestines, lungs, kidneys and macrophages (7). HCoV-229E infection is manifested by high fever, sore throat, cough, shivering, rhinitis, excessive mucous production in the bronchial tree. Additionally, headaches and myalgia are often observed while vomiting and diarrhoea – rarely. These symptoms are similar to those induced by other coronaviruses, such as OC43, HKU1, and NL63. Among four coronaviruses, responsible for upper respiratory tract infections, HCoV-229E was most frequent in China according to Lu et al. studies (8).

CORONAVIRUSES NL63

HCoV-NL63 is called a New Haven coronavirus. It was identified for the first time as bronchitis factor in a 7-month-child hospitalized in one of hospitals in Netherlands due to fever, rhinitis, and conjunctivitis. Based on numerous analyzed cases of HCoV-NL63 infections, van der Hoek et al. showed that this viral infection concerned most frequently children up to 3 years of age with coexisting diseases such as whooping cough, diabetes, myocarditis (9). Thus, it seems the virus is dangerous for children with lowered immunity.

HCoV-NL63 infections were observed in single cases of Kawasaki disease and systemic vasculitis. Coronary aneurysms were frequently observed among these patients, which can be connected with the viral infection (10).

CORONAVIRUSES HKU1

In 2004, in Hong Kong, a 71-year-old patient with pneumonia revealed a new coronavirus, HCoV-HKU1 (11), which resembled HCoV-229E in its structure. The virus is the etiologic factor of severe pneumonia with acute respiratory failure. Frequent convulsions in the course of infection are the characteristic feature of the disease. This viral infection can lead to meningomyelitis. HCoV-HKU1 occurs world-wide and winter and spring favor the infections, specifically in elderly and children. HCoV-HKU1 frequently causes superinfections in children with bacterial bronchiolitis and asthma (12), which indicates infections mainly in people with lowered immunity.

A new virus HCoV-HKU1-HN (New Haven) is very similar to HCoV-HKU1 and HCoV-NL63 as far as the structure is concerned (13). It is often isolated from patients with Kawasaki disease. Kawasaki disease is a febrile disease occurring in children under 5 years of age, it often induces various damages of the heart muscle and coronary vessels. The etiology of the disease is unknown and the role of HCoV-HKU1-NH has not been determined yet (14).

SARS

At the end of 2002, numerous cases of febrile disease with acute respiratory failure were observed in Guangdong province in the south-eastern China. The virus was isolated for the first time from the lung tissue (open lung biopsy) of a 65-year-old patient, a physician, who was in the Chinese province (15).

The incubation period varied from 2 to 10 days with early symptoms of dry cough and dyspnoea. Pneumonia occurred quickly with coexisting high fever, shivering, myalgia, sometimes diarrhoea. Intensive studies enabled to determine the pathogenic factor, the coronavirus SARS. The infection turned out to be extremely dangerous; 774 patients out of more than 8000 ones died of SARS in 2003 (15).

The first animals from which the viruses, very similar to HCoV-SARS and capable of infecting people, were isolated were civet Himalayan palm and raccoon dog. However, further studies revealed bats to be the direct source of the infection and viral vector. The virus can be transmitted from human to human.

HCoV-SARS gets to the epithelial cells of the respiratory tract and causes their damage. Like other coronaviruses, HCoV-SARS binds its protein spikes with receptors for ACE2 on the cells of the respiratory tract and only after the binding it penetrates the cell.

Sudden damage of the alveoli and accumulation of excessive amount of secretion in the bronchial tree influence rapid course of the disease which results in acute respiratory failure. Exudative changes in the respiratory tract, mainly in the alveoli, are accompanied by macrophages accumulation. This period is characterized by frequent blood escape into the respiratory tract, pulmonary oedema, hyaline membranes formation in the alveoli. Patients with the disease duration of more than 10 days develop lowered elasticity and fibrosis of the lungs (16).

Computer tomography is remarkably useful in the early diagnostics as the changes, characterized by the lowered pneumatization of the lungs or sometimes mediastinal emphysema, usually precede significantly the presence of pathological changes in the classical X-ray examination (17).

Lymphopenia, thrombocytopenia, increased activity of creatine phosphatase, lactate dehydrogenase, and aminotransferases are observed in the course of the infection.

Ribavirin is an effective drug in the early stage of the disease.

The introduction of epidemiological regime in the numerous international airports, specifically those with connection to Asia, prevented spread of epidemic. However, single disease focuses have occurred in the southern China to date.

MERS

In September 2012, Dr Ali Mohammed Zaki isolated a new coronavirus, called MERS (Middle East Respiratory Virus), from an elderly patient from Jeddah, Saudi Arabia, with acute respiratory failure due to pneumonia and kidney failure. Since the moment of the virus MERS discovery, 180 cases were confirmed, mainly in the areas of Saudi Arabia, Qatar, Jordan, Tunisia, and the United Arab Emirates. Migration from the countries of the Persian Gulf and tourism in this area are of greatest importance in the spread of the virus. The mortality equals approximately 50%. The virus has already come to Europe and first cases were noted in people coming from the United Arab Emirates to France, Britain, and Germany (18).

The probable sources of infection are certain kinds of bats and camels. However, the examinations determining the presence of specific antibodies in the sera of domesticated animals did not exclude the virus reservoir only in camels. The infection takes place by the contact with the bats saliva or nasal or rectal discharge of camels (18). As for familial infections, human-human transmission was confirmed (19). The virus shows tropism to the epithelial, mainly ciliary, cells of the respiratory tract, where it binds to DPP4 receptors with domains corresponding to viral specific protein S, which is a big strongly glycolated protein that undergoes "cutting" by cellular proteases to active subunits S1 and S2. Both subunits may undergo easy mutations that change virus pathogenicity (20). HCoV-MERS inhibits interferon synthesis, which is important in the spread of infection in the host cells and cytotoxic activity of the virus (21).

The period of virus incubation is 12 days and the first symptoms are fever, cough, expectoration, and dyspnoea. Typical clinical MERS manifestations are fever, dry cough at first, dyspnoea, myalgia, nausea, vomiting, and diarrhoea. Many patients quickly develop kidneys failure that requires dialysis (22). Thrombocytopenia is frequently observed in patients and severe diseases are observed in those with diabetes, chronic kidney, heart, and lungs damage, with hypertension, neoplastic diseases, and patients after transplantations.

At present, studies on antiviral therapy effectiveness are being performed. It seems that early IFN- α therapy can be effective in the treatment of MERS (21) and so can be antiviral cyclosporine A (23).

Both WHO and ECDC with great concern monitor the rapid spread of the virus. ECDC indicates three aspects of HCoV-MERS in Europe:

1. Nowadays, there is a slight risk of HCoV-MERS infection in UE, which can be increased by tourists and pilgrims going to the Near East.

2. There is a possibility to decrease secondary risk of HCoV-MERS transmission in UE by prophylaxis and the control of infections of patients who undergo epidemiological investigation.
3. Human-human transmission of the virus is probable, however this kind of infection is unimportant as for infection spread.

According to ECDC, tourists who travel to the Near East should:

1. Avoid animals and the contact with their excrements.

2. Avoid persons with symptoms of acute respiratory infection.
3. Strictly obey basic hygienic rules.

Currently, the criteria, that allow to announce the international risk of HCoV-MERS infection, are not fulfilled.

It is highly probable that HCoV-MERS infection can occur in case of symptoms of respiratory infection within 14 days after returning from the countries where the infection occurs.

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