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The novel Coronavirus (nCoV) – A Worldwide Threat

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Abstract

This review aims to assess the actual data from recently published literature dealing with the novel Coronavirus (nCoV) isolated in automn 2019. Similarly to the classical Coronavirus (cCoV) identified 18 years ago, also the nCoV has emerged in China, though in a different region. The large number of papers dealing with similar topics clearly points at its importance as well as at the unexpected danger for public health. Herewith the clinical signs of typical nCoV disease as well as the related pathological states are briefly outlined. Last but not least, relevant epidemiological data are presented in order to trace of the routes of nCoV spread in human population, with special regards to the region of Middle Europe. The data presented are useful not only for the understanding of coronavirus replication, but also for the description of virion structure and for interpreting its properties.

Keywords:

Coronavirus; Virion structure; Virus transmission; Clinical signs of disease

Summary

Within a relatively short period of 5-6 months (from March until September 2020) the novel Coronavirus (nCoV) has emerged in China (in the city of Wuhan, Hubei province), where from it spread all over the world. Some investigators also called it Coronavirus 2019 (CoV-19), while the others termed it Coronavirus 2 (CoV-2). In the early stages of nCoV infection cases of pneumonia have been reported, while other patients showed acute respiratory symptoms, namely the syndrome of rapidly developing acute respiratory distress (ARD) and/or acute respiratory failure, both accompanied with serious complications leading to death [1]. In a proportion of infected subjects, the less severe cases revealed clinical complaints called Coronavirus Disease (CoVID-19), an entity closely resembling to previously described severe acute respiratory syndrome (SARS) [2]. Several details of the recent nCoV/CoV-2 outbreak have still remained unclear, except for the fact that the novel virus has occurred in China and that (very probably) it has been transmitted by direct exposure. In this respect, the recent nCoV outbreak has shown a possible link to the South China Seafood market at City of Wuhan [3]. Despite of that the fish and wild animal market in Wuhan has remained in continuous performance selling live animals (such as poultry, bats, marmots and snakes), regardless that it became the source of a dangerous infection [4]. Even though the majority of CoVID-19 cases was reported in patients from continental China, also the island of Taiwan has been involved [5]. Unlike to the previously described (in late autumn of the year 2002) classical Coronavirus (cCoV), which had been isolated 18 years ago in a different Chinese province (Guandong), nCoV spread quickly infecting over 52 million people worldwide, a proportion (about 3-4 %) of whom developed signs of severe lung disease .

Due to quick spread of nCoV/CoV-2, the WHO declared the recent outbreak for a public health emergency, i.e. a situation deserving wide international concern [6]. There has been recognised that the valid healthcare measures may not be sufficient for preventing further nCoV/CoV-2 transfer. Especially the spread of CoVID-19 from asymptomatic carriers (i.e. via person-to-person contact) deserves much attention [7]. To stop such dangerous outcome, additional measures are recommended and their practical effects should be checked to reach the following goals: 1) slowing down the spread of CoVID-19 illness; 2) providing time (in any cooperating state) to implement the rules of local health care; 3) achieving an individual business protection and 4) improving the actual education of local health authorities; 5) instructing the general public how to avoid a virus transmission of disastrous extent (if possible); 6) and finally, describing the signs of CoVID-19 in the majority of local health guidelines [8].

It comes from above mentioned considerations that development and deployment of medical countermeasures, including precise diagnostics and therapeutic recommendations (not excluding the continuous efforts for vaccine development) has become into focus of interest [9]. For achieving this, especially the asymptomatic CoVID-19 cases should be assessed, based either on viral nucleic acid tests or on virus antigen detection. Infections occurring in the absence of any CoVID-19 symptoms, either respiratory or gastrointestinal, may not show any significant abnormalities on chest radiograph [10]. Guan et al. using a larger patient sample for estimation, suggested that the median incubation period might be 3 days only, but could be as long as 24 days. Noteworthy, the mean incubation time was estimated for 5.2 days, in a range from 2.1 to 11.1 days [11].

Some patients with SARS, which were defined as laboratory-confirmed CoVID-19 cases, had respiratory symptoms even though their chest computed tomography (CT) but did not reveal signs of pneumonia [12]. Another patients with pneumonia manifested on their chest radiograph (defined for CoVID-19 positive), then had both, the respiratory symptoms as well as pneumonia [13]. The latter category of positive individuals showed severe pneumonia along with a state of critical clinical conditions, such as shock and/or respiratory failure

requiring mechanical ventilation. In some cases there even was a general organ failure needing special management [14]. In general, fever occurs with a probability ranging from 67% to 98%, cough by at least from 43% but up to 81%; the shortness of breath may be present in 31% to 55% of CoVID-19 cases and finally, the frequency of myalgias remains as low as 3% to 11%, but never exceeding 44% [15]. Patients with pneumonia were older, with a higher prevalence of smoking history and more underlying diseases. They were more likely to have fever, myalgia/fatigue, dyspnea, headache, and nausea/vomiting as compared to patients with a simple ARD, revealing a statistical difference of $p < 0.05$. In addition, the pneumonia cases have presented higher white blood cell and neutrophil counts, while the simple ARD cases had rather a reduced leukocyte count [16]. The pneumonia patients, as a rule, received more antibiotics and/or antiviral therapy and later on they were more likely to require oxygenation therapy, mechanical ventilator, extracorporeal membrane oxygenation and even renal replacement [17].

Since the person-to-person transmission of nCoV has been clearly identified, the asymptomatic individuals were recognized for potential sources of infection [18,19]. The identification of nCoV cases as well as their contacts has led to the assessment of travelers arriving from areas with more frequent and/or substantial virus transmission. These conditions have got similar to and/or identical with those introduced in the course of influenza virus pandemic [20]. The differences in infectivity among the various coronavirus isolates were attributed to differences in the rigidity of their shells and/or another chosen proteins, a parameter which could be evaluated using computational tools applied for predicting any intrinsic disorder predisposition [21]. The estimated reproductive number of 0.3 was obtained from considering a small amount of infected persons who revealed not quite precise information as the onset of the outbreak concerns; therefore the reproductive number of nCoV/CoV-19 is likely to be similar to that of the SARS-cCoV appearing in 2003 during the pre-intervention period (in the range from 2 to 3) and that of the 2009 pandemic of influenza virus A/H1N1 in the United States (in the range from 1.3 to 1.7) [22]. Owing to these observations, the current control measures, namely the quarantine and an/or the observation period of 10-14 days are just appropriate.

The structural proteins (and/or glycoproteins) at any Beta-coronavirus (B-CoV) strain are encoded by four regular structural genes, namely the spike glycoprotein (S, former E2), the envelope glycoprotein (E, former sM), the membrane glycoprotein (M, former E1) and the nucleocapsid protein (N) [23]. The 29.7 kb long sequence of the single stranded negative sense viral RNA (vRNA) has an untranslated region at its 5′-end (5′- UTR) along with a short leader sequence (LS) which continues into the two relatively long open reading frames (ORF 1a/b) encoding the corresponding polyproteins (Plp1a and Plp1b). These both become cleaved by an endogenous peptidase to form at least 13-15 non-structural polypeptides (NSP) involved mainly in vRNA replication. Another four genes encoding structural proteins are interrupted by regions specifying the so called accessory proteins (in the case of CoV-2 these are the following: ORF 3a, ORF 3b, ORF6, ORF7a, ORF7b, ORF 8a, ORF 8b and ORF9). Some of these are located in between S and E sequences (ORF 3a/3b), but the majority between the M and N genes (with exception of ORF 9 which is positioned within the N sequence). The vRNA ends with a short untranslated region of the 3′-UTR sequence.

When comparing the CoV-2 with earlier isolated CoV strains, a key variation was found in the ORF 3 sequence region. The life cycle of CoV-2 in the susceptible host cells begins by binding of S protein to corresponding cellular receptor, namely the angiotensin converting enzyme 2 (ACE2). After receptor binding, a conformation change within the S protein facilitates the fusion of virion membrane with the cell membrane, an event which activates the transportation pathway along the cellular endosomal reticulum (ER). The virus coded polymerase produces a series of sub-genomic mRNAs transcribed from the released vRNA by a process called discontinuous transcription. In the region of cellular ER and Golgi apparatus the set of newly formed transcripts is finally translated into relevant viral proteins. These along with the transcribed novel vRNA are subsequently assembled into new virions, which are via the cytoplasmic vesicles transported back to cell membrane in order to get released out of the cell.

There is no clinically approved antiviral drug or vaccine available to be used against CoVID-19. As of now, there is no specific antiviral medication available for CoVID-19 treatment, neither is currently a safe vaccine available. For patients with severe infection, the health care providers generally recommend to treat the symptoms by using oxygen therapy. However, a few broad-spectrum antiviral drugs have been evaluated as well. For example, for potential antiviral treatment of human nCoV drugs such as Lopinavir/Ritonavir (400 mg/100 mg per dose) have been recommended. In addition, nucleoside analogues, neuraminidase inhibitors, Remdesivir, the peptide EK1, arbidol, RNA synthesis inhibitors (such as TDF, 3TC) and/or certain anti-inflammatory drugs including IFN-alpha (5 million Units/dose) were tested. IFN-alpha is a broad spectrum antiviral substance, which has been used, to treat hepatitis B. Lopinavir is a protease inhibitor showing anti-CoV activity in vitro. It has been used to treat infection by human immune deficiency virus (HIV), together with Ritonavir as a booster. For SARS treatment, there was found that in contrast to Ribavirin alone, patients treated with Lopinavir/Ritonavir as well as Ribavirin had a lower risk of the ARD syndrome and/or death. Namely Ribavirin can effectively reduce the virus titer in experimental infection of mice improving the lung tissue damage. The effect of the latter drug combination may be better than the treatment using Lopinavir/Ritonavir along with interferon [24]. As shown in mice infected with a previously isolated CoV causing the so called Middle East Respiratory Syndrome (MERS), Remdesivir may have the best CoV treatment potential. The MERS-CoV was first identified in 2012; since then over 400 cases were registered. The cell receptor for MERS-CoV is the dipeptidyl peptidase 4 (DPP4/8CD26), while dromedary camels are believed to be the reservoir for virus transmission.

China has relied on the use of the anti-viral drug Favilavir to treat the symptoms of CoVID-19. This medication was initially developed by Toyama Chemical to treat nose and throat infections. Although the results of the study have not yet been published, it has been assumed that the drug has proven effective (at least in part) in treating symptoms of CoVID-19 in a clinical trial of more than 70 patients with minimal side effects. Favilavir was approved in Japan in 2014 to treat influenza, but currently it has been also used for treating CoVID-19 [25], but not by the U.S. Food and Drug Administration (FDA). Remdesivir (GS-5734) is a broad-acting antiviral drug originally designed to target Ebola as it had been developed by Gilead Sciences. Remdesivir inhibits viral replication through premature termination of vRNA transcription, i.e. by disrupting virus reproduction. China announced that the clinical trials for Remdesivir have been officially started in Wuhan by testing its efficacy against CoVID-19; an additional single clinical trial has been approved by

FDA in United States. However, the efficacy and claiming safety of Remdesivir still needs further clinical trials. Chloroquine and Hydroxychloroquine, drugs used to treat malaria and arthritis, respectively, were recommended by the National Health Commission of the People's Republic of China CoVID-19 for treatment. As mentioned above, Chloroquine and Hydroxychloroquine are drugs used to treat malaria, as well as chemoprophylaxis; and certain inflammatory conditions to include rheumatoid arthritis, lupus and a rare blood disorder called porphyria cutanea tarda. They have been approved by the U. S. FDA to be tested against CoVID-19. Researchers have found that both drugs have in vitro activity against cCoV as well as nCoV/CoV-2, with Hydroxychloroquine having a relatively higher potency. Based on these results, Chloroquine and Hydroxychloroquine are currently recommended for treatment of hospitalized CoVID-19 patients in several countries, including in the U. S. One Chinese study showed that when Chloroquine was tested on more than 100 patients, it had superior results compared to a control drug inhibiting the exacerbation of pneumonia, improving lung-imaging findings, promoting virus negative conversion and shortening the disease course. However, both Chloroquine and Hydroxychloroquine cause frequent side effects, such as worsening vision, nausea, digestive disorders and in more severe cases can lead to heart failure. As recently reported, a man in Arizona died and his wife was in critical condition when taking Chloroquine just prophylactically in order to prevent CoV-2 infection.

Lopinavir/Ritonavir are sold by AbbVie under the name Kaletra; originally they have been designed to treat the acute immune deficiency syndrome (AIDS). To evaluate the efficacy of Lopinavir/Ritonavir for CoV-2 infection, 99 patients with positive tests were treated with given drug combination. Surprisingly, no benefit as compared to the standard care was observed in latter study [26]. However, in South Korea, a 54-year-old man who was given a combination of these two medications had a significant and substantial decrease in the levels of the Beta-coronavirus. According to the WHO, there may be benefits when using Lopinavir/Ritonavir in combination with additional drugs such as interferon-β, Oseltamivir and/or Ribavirin. As above described, the treatment of SARS and MERS has been mainly focused on using drugs with more general antiviral activity, rather than on data obtained at experimental therapy of animal infection models such as primates or rodents [27].

The immune response is expected being similar to that described for other coronaviruses. Given its activity on the interferon pathway, and the manner in which it dysregulates innate immunity, the use of additional treatments directed at modulating or containing this could be of interest. Furthermore, circulating SARS-CoV-2-specific CD8+ and CD4+ T cells were identified in 70% and 100% of COVID-19 convalescent patients, respectively. CD4+ T cell responses to S protein, the main target of most vaccine efforts, were robust and correlated with the magnitude of the antiSARS-CoV-2 IgG and IgA titers. The M, spike, and N proteins each accounted for 11%–27% of the total CD4+ response, with additional responses commonly targeting certain non-polypeptides, such as nsp3, nsp4 as well as the proteins encoded by ORF3a, and ORF8 [28].

The leading cause of mortality in CoVID-19 patients is the cytokine storm syndrome associated with inflammation. The CoVID-19 patients might have higher levels of several pro-inflammatory cytokines and chemokines. Namely, the blood laboratory profile of CoVID-19 patients exhibits lymphopenia, leukopenia, thrombocytopenia, and also RNA-emia, along with the increased levels of aspartate aminotransferase. It should be noted that SARS-CoV-2 infection in pregnant women does not lead to fetus mortality, unlike to other coronaviruses, i.e. the classical SARS-cCoV and/or the MERS-CoV. Thus, to date there is no evidence for intrauterine transmission of SARS-CoV-2 to neonates [29].

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