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Host Factors That Aggravate COVID-19 Pneumonia

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Abstract

The cumulative number of COVID-19 patients per 100,000 population units varies between countries: Spain and Italy have more than 30, many European countries have between 10 and 20, and East Asian countries have 0.1 to 0.3. Various host factors can influence the mortality, but innate immunity prevails at the initial stage of infection. IgA and secretory IgA are responsible for the immunity in the oral cavity and intestinal tract. IgA deficiency is common in Europe and the United-States, while it is very rare in Japan. This difference may explain differences in the number of deaths by COVID-19. Developing countries will remain affected by the pandemic for a few more years. Predicting severity is important, and sIgA measurement in saliva seems to be simple and cost-effective. Intestinal Microbiota and metabolites like butyrate are also related to the innate immunity. Brown rice eaters show an ideal symbiotic composition of Microbiota to build innate immunity.

Introduction

Different mortality rates by COVID-19 infection

COVID-19 pneumonia was first reported in Wuhan, China in December last year. By the end of January, when WHO declared a "public health emergency of international concern", it had spread to 114 countries, the number of infected people reached 118,000 and the number of deaths reached 4,200 [1,2].

By the end of April, the coronavirus SARS-CoV-2 had infected more than 3.1 million people and killed more than 210,000 people in more than 150 countries. As of May 1, the number of infected people in Japan was 14,553 the number of deaths was 486, notably less in comparison to other countries after similar onset intervals [3]. Typically, PCR-positive cases have been considered as confirmed, but in April, antibody positive persons were also counted as infected, although the sensitivity of PCR and antibody tests are still in debate [4,5].

Daily WHO situation reports show the absolute number of new cases and deaths, but it is necessary to adjust the number of cases by the population of each country in order to compare the magnitude of cumulative incidence rates [1].

Using the United Nations Population Division data to calculate the cumulative number of patients per 100,000 population units, Spain and Italy have more than 30, many European countries such as France and Britain have between 10 and 20, and East Asian countries, (the Republic of Korea, China and Japan) have 0.1 to 0.3. The incidence in Japan is thus very small compared to Western countries.

Is the infectivity of the virus different depending on the region, or is there a genetic difference in susceptibility?

In a previous paper, I suggested that SARS-CoV-2 could be a mildly virulent virus that already coexisted with humans for some time (like herpes), because symptomatic disease was mostly seen in the elderly [6]. Coronaviruses are emerging almost every eight years, as seen with the succession of SARS (Severe Acute Respiratory Syndrome), MERS (Middle East Respiratory Syndrome), and COVID-19. The SARS mortality rate was 9.6%. For MERS, it was 41% in Saudi Arabia and 20% in South Korea. The mortality rates of COVID-19 are very high in Italy and Spain, compared to other regions. According to EU reports, the virus itself has already mutated and split into more than 10 clades [7-9]. The Japan National Institute of Infectious Diseases reported that the Wuhan virus infection made the first wave of infection in Japan, while the virus currently circulating in a second wave was introduced from Europe [8]. If mutants appear one after another, there will be difficulties

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to produce conventional vaccines. Deaths in the United States seem to affect predominantly undernourished and obese black people, patients who live in air-polluted areas also reportedly linked to low income and poor living conditions show a higher mortality [10]. On the other hand, there are quite a few people who do not develop the disease even after being infected with the virus. It is believed that these individuals are capable to rapidly mount an effective innate immune response [11].

Coronavirus infection and host response

A characteristic feature of COVID-19 infection is that the virus stays in the nasopharyngeal epithelia for a few days without apparent manifestation after entering the body. This latency seems to be due to interferon and antiviral factors working inside and outside the infected cells. SARS-CoV-2 binds to Angiotensin-Converting Enzyme 2 (ACE2) receptors found in abundance in airway epithelial cells. Host cell proteases then cleave the spike glycoprotein, releasing nucleocapsid and viral RNA into the cell, to initiate the synthesis of virus proteins (Figure 1). Viral RNA and proteins assemble to make new infective particles [12-14].

Initial response in the infected cells, activation of the local innate immune system by cytokines from dendritic cells, macrophages, and NK cells occur, and then switch to the immunoglobulin synthesis. Over secretion of cytokines and chemokines may cause cytokine storm in conjunction with vascular leakage and mast cell infiltration. If inflammation expands to the intestine, it stimulates the Gut Associated Lymphoid Tissue (GALT). Secretory IgA (s-IgA) plays an important role in immune response, as well as IgM and IgG. Balance of T17 and Treg is important to control the immune response, and intestinal Microbiota and their metabolite like butyrate also contribute to keep the balance.

During this process, intracellular antiviral accessory factors and type-1 interferon in the cells are activated. MicroRNA could also participate in the control of viral replication [14-16]. Eight percent of the human genome constitutes so-called endogenous viral elements, and they seem to be responsible for RNA-mediated immunity. MicroRNAs may control the transcription of viral RNAs, but this is still to be proven. MicroRNAs might be activated earlier than the adaptive immune system, thus suppressing the onset of virus infection [17,18].

The fact that 80% of infected people have mild symptoms, and only 20% develop a severe condition may be related to the activity of ACE2 protease, the first encountered host factor. If the initial cleavage is fast, the virus can easily spread to the whole body before immune response takes control [14]. It may correspond to "wide range of symptoms" that ranged from "mild symptoms to severe illness". Several factors are considered to affect the early lesion.

Chronic inflammatory lung diseases are associated with higher-than-normal levels of proteases. In the case of infectious diseases, laboratory research prevails, but epidemiological studies on host factors should not lag behind. This time as well, the elderly and people with illnesses such as diabetes and heart disease were reported as high risk, but the pathologically convincing causal relationship was not shown [6]. When the infection occurs on the taste and olfactory sensory cells, it causes ageusia (loss of taste) and loss of smell sensation (anosmia). When infected cells are swallowed downward, virus expansion may cause gastritis and/or enteritis with diarrhea or other gastrointestinal manifestation.

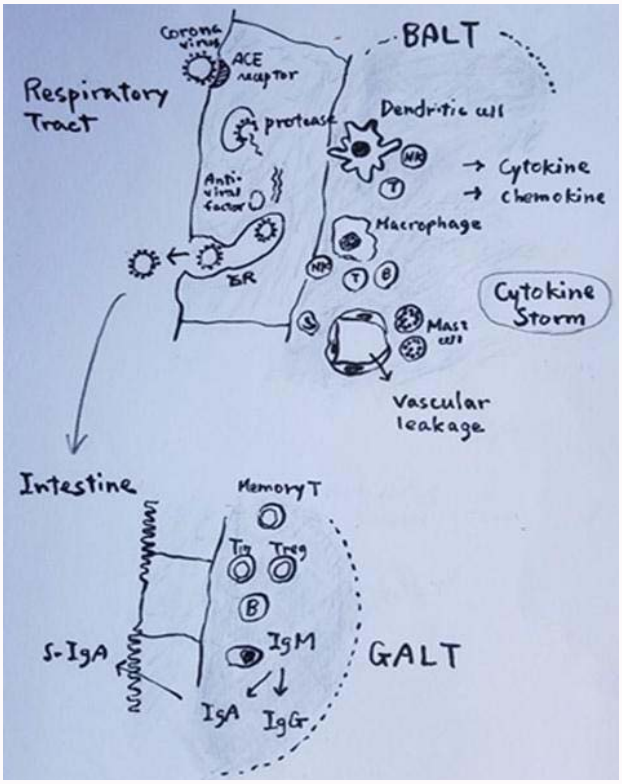

Figure 1: Pathophysiology of corona virus infection.

The severity of pneumonia is related to the low oxygen consumption of the blood. As viral infection causes alveolar interstitial edema and inflammatory exudates, oxygen exchange is disturbed, with increased capillary resistance and high pulmonary blood pressure. As a result, cardiomyocytes and blood circulation are compromised.

In such cases, oxygen delivery systems or mechanical ventilator should be used. ECMO (Extracorporeal Membrane Oxygenation) is also used for severe cases, but only 100 out of 1,500 machines are used in Japan because of the lack of skilled human resources and money.

Sudden worsening is considered to be due to cytokine storm, which is triggered by the overproduction of interferon. However, there are only few reports of autopsy that could confirm the presence of systemic lesions in the whole body.

About 10 to 14 days after infection, antibodies become detectable and virus-specific PCR becomes negative. There are reports of patients with severe pneumonia recovering after infusion of convalescent serum [19-22]. However, the risk and frequency of re-infection are still unknown. Furthermore, the presence of detectable antibodies in the blood does not necessarily indicate protection against respiratory tract infection.

IgA deficiency and severity of COVID-19 infection

Serum IgA and secretory (s-IgA), are responsible for the immunity in the oral cavity and intestinal tract [23-25]. It is noteworthy that there are big genetic differences in IgA activity between populations. Diarrhea and other gastrointestinal symptoms occur in about 10% of people with SARS-CoV-2 infection. The infected pharyngeal epithelium may fall into the digestive tract along with saliva, and infection may be established when the intestinal immunity is weak.

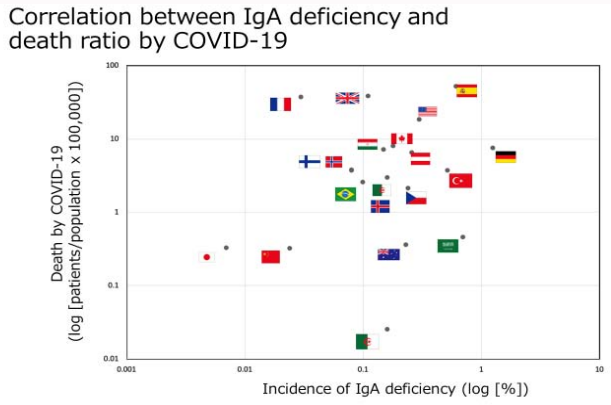

Figure 2: Correlation between secretory IgA deficiency and death ratio by COVID-19.

IgA has a secretory form, and IgA deficiency is common in Europe and the United States compared to the Orientals. This difference may explain the differences in the number of deaths by COVID-19 (Figure 2). For example, the relative proportion of individuals affected by s-IgA deficiency varies between: 1 in 143 in the Arabian Peninsula, 1 in 163 in Spain, 1 in 252 in Nigeria, 1 in 875 in the UK, 1 in 965 in Brazil, 1 in 223 to 1000 in the United States, while the proportion is 1 in 2,600 to 5,300 in China, and 1 in 14,840 to 18,500 in Japan. In particular, Caucasians and Africans have tens to 100 times more IgA-deficient people than Japanese, and Chinese were intermediate between Japanese and Western. The findings seem to be well correlated with the variable patterns of outbreaks seen within this new coronavirus.

S-IgA production is significantly lower in allergic patients (cedar pollinosis, perennial rhinitis, atopic dermatitis, asthma). Yamamoto [26] found that allergic people have influenza infection rates significantly higher than healthy subjects. In other words, low s-IgA level is one important factor for the risk of respiratory tract infection.

IgA-deficient people have the same levels of IgG and IgM as those of the healthy people, and they are living as usual without any symptoms. However, recent studies revealed that once respiratory infections occur, 20% to 30% of them develop severe symptoms. It is said that Japanese people have more side effects of dry cough than Westerners when using ACE2 receptor antagonists, which may also suggest a difference in receptor expression.

Elderly high risk people

This time as well, the elderly and people with illnesses such as diabetes, hypertension and heart disease were reported as high risk, but no convincing causal relationship has been demonstrated [6]. It is assumed that those elderly people with poor prognosis already have lung damage due to smoking, obesity, or other co-morbidities. Cigarette smoking inevitably harms the lungs. It seems that the number of people who have no symptom after SARS-CoV-2 infection is expanding, so it is no longer possible to trace contacts. In this case, the innate immune system is the main protection through BALT (Bronchus-Associated Lymphoid Tissue) and GALT (Gut-Associated Lymphoid Tissue) immune barriers. In particular, the intestinal lymphatic apparatus has a close interaction with short-chain fatty acids and intestinal bacteria, affecting the whole body [27]. Kenya Honda et al. [28] have identified and isolated 11 types of enterobacteria (11 strains) that activate immune cells called CD8 T cells from the stools of healthy subjects. When cocktails of these 11 strains are administered to aseptic mice, resistance against pathogenic bacteria and anti-cancer properties are enhanced. Brown rice eaters have most of these bacteria and show an ideal symbiotic composition. Immune control by regulatory T cells (T_{reg}) seems to be important to avoid a cytokine storm [29]. The occurrence of diarrhea in about 10% COVID-19 patients is a reflection of the immune function in the intestinal tract. A large-scale diet and health cohort study conducted by the National Cancer Center Group enrolled 140,000 people in 11 health centers nationwide, and recorded 13,000 deaths during the 15-year follow-up period. Intake of soybean foods, tofu, miso and natto seemed to correlate with a reduced mortality of about 10%. Miso soup is usually taken with rice [30]. The Medical Rice Association recommends eating brown rice, miso soup, and the main and side dishes as a basic diet [31]. Above all, there is no constipation, and the shape of the stool is good. These are good signs of intestinal environmental. When Microbiota profiles were compared between brown rice and white rice eaters, the former harbored more frequently butyrate-producing bacteria and less frequently *fusobacterium* species. High prevalence of *Faecalibacterium prausnitzii* suggested the benefit on butyrate production, and Blautia wexlerae suggested the control on intestinal immunity.

Exit strategy

SARS-CoV-2 is bound to stay with us for some time, and it is now better to look for methods of coexistence rather than aim at absolute control of corona virus [32]. Dozens of clinical trials of therapeutic drugs and vaccines have begun, but results will not appear before a year or two. In the meantime, the key would be to strengthen our innate immunity. There are many viruses that coexist with humans, such as herpes, HPV, and hepatitis C. Accepting coronaviruses SARS-CoV-2 as a part of the biosphere and focusing on preventing complications by the immune system are reasonable ways to explore. Predicting severity is important, and sIgA measurement in saliva seems to be simple and cost-effective.

The COVID-19 pandemic reminds us of the power of wellbeing. In the US, victims are typically poor people, who could not afford to go to hospitals and could not receive medical services. Understaffed medical facilities are grounds for nosocomial infections, and have seen many doctors and nurses infected themselves.

Public health funding by stakeholders has been cut after "money first" policies and social requirement to welcome. Distressing clinical triage schemes were introduced in some countries. Communication technologies could support social networks systems between people staying at home. But it is only possible in developed countries.

Could we figure out the post-COVID19 world? Developing countries will remain affected by the pandemic for a few more years. Keeping social or physical distances will disturb social norms of interactions with neighbor people, and even between family members.

"Diversity and harmonization" was declared a priority at the 12th Asia Pacific Conference of Clinical Nutrition in Nanjing to focus on minorities and vulnerable people who should be protected from the harms of international capitalism.

COVID-19 may cause collapse of the society, but if this can be avoided, it could be an opportunity to create independent communities with self-sufficiency and modest life, co-existing with nature to give us a safer and happier life.

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