WHY COVID–19 IS LETHAL TO ELDERLY AND CHRONICALLY ILL?

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ABSTRACT

Our work consists of a systematic statistical approach and analysis of the pathophysiological literature review of the Coronavirus 2019.Firstly, we have given a realistic view of the re-emerging disease caused by the Coronavirus through the detailed information available, and secondly, we have given probable explanations based on old literature and research on the specific immune profile and the dangers related to age and chronic diseases. Systematic analysis of the data shows the relationship between age and chronic disease with CoVID 19 mortality, the closest explanation for this relationship is the phenomenon of the 'Cytokine storm', where the immune system acts reversibly on older people or people with chronic diseases. The suggestion obtained from this study is that at this point for this pandemic it is necessary to work only on the symptomatic treatment of cytokine shock in this population because even after having a vaccination for the virus the risk remains significant for them.

Introduction

Coronaviruses were named based on the crown-shaped aspect of their virions as viewed under electron microscopy. These viruses are the second commonest cause of the common cold, with rhinoviruses being the primary culprit. (Stadler et al., 2003)

It has also been reported that coronaviruses induce gastroenteritis in children and adults (Clarke et al., 1979); in 2002 Severe Coronavirus Associated with Acute Respiratory Syndrome (SARS) (Goldsmith et al., 2004) and (SARS-CoV 2) is a newly described coronavirus in 2019. (Lai et al., 2020; Berghiche, 2020).

The virus produces atypical pneumonia, serious illness, and potentially fatal viral infection in humans, it is strictly confined to the mucosal cells of the airway. (Poon et al., 2004).

The virus generally causes infections of the superior respiratory tract, as the optimal temperature for virus replication is 37-38°C. The envelope contains (a) viral binding protein E2, (b) matrix protein E1, and (c) nucleocapsid protein N1. In the early phase of infection produces RNA polymerase; the late phase produces non-structural proteins from a negative- sense RNA template. CoVid 19 causes an airway infection by binding to angiotensin-2 converting enzyme receptors on the surface of the respiratory epithelium. (Shereen el al., 2020;Memish et al., 2020; Han et al., 2020).

This causes an alteration of the water balance and leads to the development of alveolar space edema, which diffuse edema leading to hypoxia is characteristic of pneumonia caused by this virus, we must note that the infections caused by coronaviruses produce a brief immunity, but reinfection may occur. (Jin et al., 2020; Piccoli, 2020; Kuljić-Kapulica,2020).

Inflammation is the set of reactive defense mechanisms by which the body recognizes, destroys, and eliminates all foreign substances. The inflammatory reaction sometimes exceeds its objectives, causing deleterious effects, but this is the price the body sometimes has to pay to maintain its integrity. Grodzinsky et al., 2020).

The causes of inflammation are many and varied: infectious agent, inert foreign substance, physical agent, post-traumatic lesion of cyto-tissues, etc. Inflammation begins with a "recognition" reaction involving certain cells in the body (monocytes, macrophages, lymphocytes) or circulating proteins (antibodies, complement proteins, Hageman factor, etc.) (Goldstein et al., 1992).

The recognition phase is followed by the sequential involvement of a whole set of cells and mediators whose order of intervention is complex and variable. Some mediators, such as prostaglandins and cytokines, are produced by different cell types, act on several cell types, and sometimes control their production by retroactive regulation. This shows the complexity of the mechanisms of the inflammatory reaction, which prevents the description of an overall pattern and requires an analytical and individual description of the cells and the mediators that make it up. (Sedger et al., 2014).

The cytokine is a low molecular weight secreted proteins that regulate the intensity and duration of innate and acquired immune responses with multiple biological properties on different cells-pleiotropy as synergy and antagonism its action (outcome) depends on receptor being present it can be autocrine, paracrine or endocrine. (Klasing and Korver, 1997;Janeway *et al.,* 1999).

Broad Categories of Cytokine Function are Cytokines that mediate and regulate innate immunity; Cytokines that mediate and regulate specific or adaptive immunity and Cytokines that stimulate hematopoiesis. (Abbas *et al.,*1997).

The immune system is our defense. In addition to

its protective role against external aggressions, the immune system plays a key role in the internal balance of the organism. Unfortunately, this system sometimes gets it wrong and attacks the body's constituents. (Nicholson, 2016).

The elderly is more prone than the young to suffering from an illness (for example, pneumonia) and have a high mortality rate. (Gardner,1980) measles, myelin, poliomyelitis, and CoVid 19 are examples of diseases that cause more serious clinical problems.

The inflammatory reaction sometimes exceeds its objectives, causing deleterious effects (Siegrist, 2007), but this is the price the body sometimes has to pay to maintain its integrity, could this be due to a more active immune response in an adult that causes increased tissue damage?

Current status data

Using data from the report of the joint WHO-China mission (WHO, 2019) and the article from the Chinese CDC (CCDC, 2020), these two sources we provide the following statistics on age and comorbidity (Worlodmeter, 2020).

Fatality ratio = (number of deaths / number of cases) = odds of mortality in case of virus infection (%).

The graphical representation shows that mortality is very directly related to the age where most deaths are over 50 years old and the very high rate corresponds to people over 80 years old.

This probability differs depending on a pre-existing condition. The interpretation of this graph shows that all the dead cases have a chronic disease, the highest rate for cardiovascular diseases, followed by diabetics, chronic respiratory diseases, and cancer patients.

The previous results give us three questions to answer:

*Why mortality rates among the elderly are the highest?

*How chronic diseases lead to a higher mortality rate for those affected?

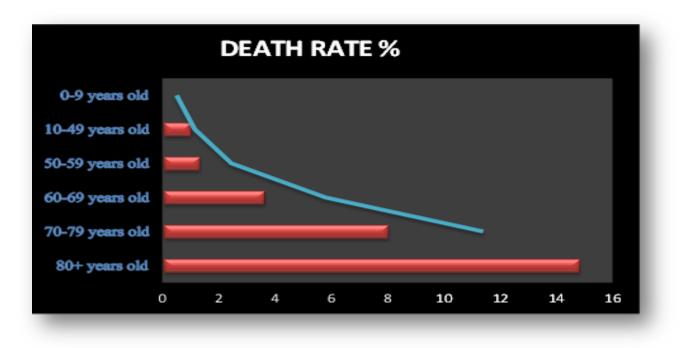*Immunity can have a negative role among elderly and chronically ill?

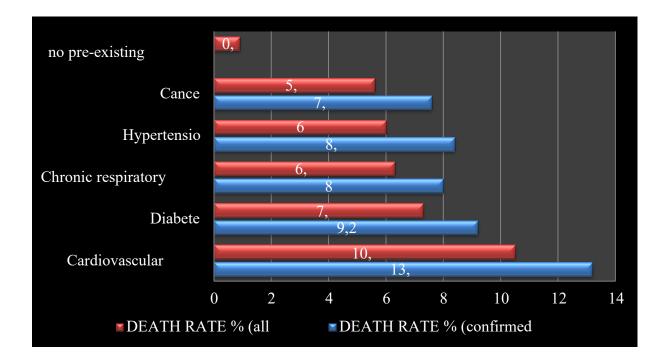**FIGURE 1: mortality rates by covid-19 classified by age**

Figure 2: COVID-19 Mortality Rate by Comorbidity

Death Rate = (number of deaths/number of cases)

Age and immunity

Immunosenescence is the process of deterioration of the immune system over time; Studies show that immune aging is associated with a higher frequency of infections, cancers, and autoimmune diseases. (Pera et al., 2015)

Immunosenescence has been linked to an increase in respiratory and urinary infections, endocarditis and sepsis (the presence of bacteria in the bloodstream) in the elderly, in cases where the infection is due to an intracellular microorganism, such as tuberculosis, legionellosis, etc., it has been noted that as one age, the microorganism that was latent in the cells and that was probably treated at the time of the first infection reactivates. An age-related decrease in the cytokine TNF-α and CD8+ T cell levels could explain the body's inability to keep these intracellular microorganisms under control and thus the frequency of these diseases in the elderly. In the case of extracellular pathogens, the increase in infections could be due to an age-related decrease in the phagocytic activity of macrophages and other granulocytes. (Ginaldi et al., 2001; Hakim and Gress, 2007)

The increase in morbidity due to the decline of the immune system is a direct consequence of the deregulation of adaptive immunity in the elderly. The low number of naive T cells compared to T cells is a consequence of the reduction in thymic production, as the thymus has regressed. As a result of this age-induced lymphopenia, T cells proliferate and increase the 'virtual memory' compartment, but at the same time, the ability to establish immunological memory in response to de novo antigens is reduced, compromising vaccinations. Functions such as the production of cytokines by CD4 and CD8 T lymphocytes are impaired, the expression of surface key markers, and the CD4 + to CD8 + ratio is reversed. The development of T lymphocytes which control latent viruses such as EBV and CMV, reduce the space for CD8 + T lymphocytes specific for other potentially fatal viruses, all of this increased by the decrease in the production of naive T cells of thymic origin. (Tarazona et al., 2002; Globerson and Effros, 2000).

Probably the most critical change as the aging innate immune system ages is the increase in the pro-inflammatory cytokines IL-1β, IL-6, IL-18, and TNFα. The resulting low-grade inflammation likely contributes to atherosclerosis, dementia, and cancer, inextricably linking inflammation and the aging of other tissues. (Simon et al., 2015; Müller and Pawelec, 2014; Di Benedetto and Müller, 2019).

Chronically ill and immunity

People with certain hormonal abnormalities are increasingly at risk of infection. For instance, people with diabetes mellitus, hypothyroidism, and adrenal dysfunction are highly sensitive to staphylococcal infections, streptococcal infections, candidiasis, aspergillosis, zygomycosis, and many other microbial infections. (Castle, 2000; Castle et al., 2007).

Cardiovascular diseases

The cardiovascular diseases are the affections that affect the heart more than those that affect the blood vessels. Cardiovascular diseases include angina, myocardial infarction, or stroke, these diseases are either congenital or acquired which mostly caused by atherosclerosis. (Ylä-Herttuala et al., 1996; Sherer and Shoenfeld, 2006).

The inflammatory response is a useful process for fighting disease. When this mechanism is strong, infection occurs very effectively. Unfortunately, in other types of inflammatory processes, such as the response to the presence of cholesterol in blood vessels, the mechanism is amplified, causing lateral damage. (Fernández-Sánchez et al., 2011; Vodovotz et al., 2009).

Inflammation and immune response are involved in the pathogenesis of atherosclerosis from the earliest stages and can influence the onset and outcome of acute coronary syndromes. The different components and phenotypes of the immune-inflammatory response can play both protective and deleterious roles. Individual variation in immune reactivity, but also different environmental factors, may reflect the ability of some individuals to produce a protective and effective immune response while others have a deleterious immune response. (Caligiuri, 2004)

Interferences and interactions between cholesterol metabolism and inflammatory pathways have a potential influence on the genes associated with these two processes. For example, in the network model, immune cells called macrophages turn into foamy cells when they absorb oxidized LDL cholesterol particles, the initial stage of plaque formation. In turn, the foam cells secrete substances called "cytokines" that stimulate the inflammatory response. (Paquette et al., 2007; Baldrighi et al., 2017)

Diabetes

It is an autoimmune disease characterized by the destruction of insulin-producing beta cells by T cells in the immune system. (Gillespie, 2006)

T lymphocytes, B lymphocytes, macrophages, neutrophils, and dendritic cells are part of a set of cells making up our immune system. They perform specific functions and act in a cooperative and very organized manner to ensure the balance of our immunity. (Sallusto et al., 2000)

In the case of type 1 diabetes, studies have described the intervention of immune cells in triggering the disease. Thus, in the absence of macrophages responsible for eliminating the remains of beta cells that die naturally or following an infection, debris from dead cells accumulates and attracts other types of immune cells and among them, the dendritic cells which present the antigens from this debris to the T lymphocytes. (Roep, 2003).

The dendritic cells also release molecules that trigger the inflammation process; those cells, therefore, come into contact with the T lymphocytes which recognize the antigen and thus target the beta cells of the pancreas and destroy them, since they are considered as a foreign body to be eliminated.

B lymphocytes also participate in this offensive by producing antibodies directed against specific components of the pancreas or against insulin itself. (Banchereau and Steinman, 1998; Rabinovitch and Suarez-Pinzon, 1998)

All these interactions between cells of the immune system, therefore, lead to the destruction of pancreatic beta cells.

This autoimmune reaction takes place in a particular context linked to the genetic predisposition or a triggering environmental factor. It spans several years before the onset of diabetes. (Van den Driessche et al., 2009; Katsarou et al., 2017).

In type 2 diabetes, the immune system is involved in the chronic activation of the phenomenon of inflammation, which is harmful in the long term for the cells. **(**Donath et al., 2009)

The molecules responsible for the activation of inflammation are strongly present in the tissues of type 2 diabetic patients. They participate in the decrease in the sensitivity of the muscles and the liver to the action of insulin. This phenomenon called insulin resistance causes the accumulation of glucose in the blood. (Osborn and Olefsky, 2012)

These so-called pro-inflammatory molecules also act on the pancreas. Their presence disrupts the functioning of beta cells and therefore the production of insulin which will be greatly reduced (insulinogenic). **(**Bailey, 2018).

The presence of inflammatory molecules seems to be greatly increased in the event of obesity. Indeed, under normal conditions, there is a balance between the production of molecules promoting inflammation and so-called anti-inflammatory molecules (Balistreri et al., 2010). Adipose tissue cells upset this balance by promoting the production of proinflammatory molecules. **(**Cersosimo et al., 2018; Sun et al., 2012).

Chronically respiratory diseases

The pulmonary affections also called pneumopathies are numerous and non-exhaustive, we have chosen three very common diseases.

Chronic bronchitis is the inflammation and exaggerated secretion in the mucous membranes of the bronchi (the layer of cells protecting the inside of the bronchi on contact with air). (Sethi, 2000)

Asthma corresponds to a particular form of dyspnoea (difficulty breathing), and more particularly to exhaling (expelling air from the lungs). There is a decrease in the size of the bronchial tubes, among other things. (Cartier,1994).

Pulmonary emphysema is a chronic (progressive) disease of the lungs characterized by the destruction of the pulmonary alveoli, resulting in distension of the alveolar walls. (Shapiro and Ingenito, 2005; Heppleston and Leopold, 1961).

The presence of a chronic respiratory disease such as chronic obstructive pulmonary disease or a disease that weakens the immune system increases the risk of CoVID 19 for the patient will develop it faster. **(**Lai et al., 2020)

Cancer

Inflammation is activated every time tissue is attacked. One of its missions is to promote the reconstruction of damaged tissue. This aspect of the inflammation is diverted by the tumor to progress to a more advanced stage. (Ran and Volk-Draper, 2020; Johnson, 2020).

However, inflammation can act against the tumor by recruiting immune system cells, some of which are responsible for eliminating cancer cells. To divert the inflammation to its advantage, the tumor may create a local environment, called the tumor microenvironment, which undermines the anti-tumor immune response. (Annibaldi and Walczak, 2020).

At the tissue level, the tumor is not just a cluster of cancer cells but a collection of both cancerous and healthy cells associated with the tumor that contribute to its development, such as endothelial cells, macrophages, and fibroblasts, this association of different cells forms a complex environment that evolves according to the behavior of the cells that make it up: this is the tumor microenvironment (Cassetta and Pollard, 2020; Blagih et al., 2020).

Healthy tumor-associated cells make an essential contribution to the development of a tumor by providing functions that cancer cells do not possess or by stimulating capacities that cancer cells have acquired (Beltraminelli and Palma, 2020; Pang et al., 2020).

Conclusion

Inflammation is a complex process involving several types of immune cells, clotting proteins, and signaling molecules, all of which change over time.

In a normal state, the inflammation will disappear on its own once irritation has subsided and the body is adequately protected. In some cases, the inflammation becomes a disease; this leads to problems with organ function and even complicity in infectious diseases or long-term inflammatory conditions

"Cytokine storm" is the pathological form of inflammation, and although the general concept of excessive or uncontrolled release of pro-inflammatory cytokines is well established, this concept and the biological implications of overproduction of cytokines are not well defined. But it is associated with a wide variety of infectious and noninfectious diseases. The "cytokine storm" is the pathological form of inflammation, and although the general concept of excessive or uncontrolled release of pro-inflammatory cytokines is well established, this concept and the biological implications of overproduction of cytokines are not well defined. But it is associated with a wide variety of infectious and non-infectious diseases. The term has been widely promoted in the context of infection with the H5N1 avian influenza virus, which has led to its inclusion in the popular media.

Cytokine storm syndromes (CSS) are a group of disorders representing a variety of inflammatory causes. The primary symptoms of a cytokine storm are high fever, swelling, and redness, extreme fatigue, and nausea.

In some cases, the immune response can be fatal in the elderly where the immune profile has been compromised and its control will be difficult in infectious diseases, also in cases of chronic diseases associated with inflammatory conditions or which act directly on the immune system; At this level, the new coronavirus has proven that human immunity can induce death.

It is recommended to treat the disease symptomatically with therapeutic interventions that target the mechanisms of inflammation such as anti-leukotriene and pro-inflammatory cytokine inhibitors.

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