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Is IL6 gene polymorphism predictor marker for severe illness and deaths among healthy adults who get sick by COVID-19 infection?

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Conflict of interest:

I declare that I have no conflict of interest.

Abstract:

COVID-19 is the disease caused by a novel coronavirus called SARS COV2. The most common symptoms are fever, dry cough and fatigue. More severe symptoms include shortness of breath, reduce consciousness, neurological complications such as stroke, brain inflammation, cardiac problem, lever dysfunction and systemic hyperinflammation with multiorgan failure and death. 80% of patients recover from covid19 without need to hospital admission.

About 15% become seriously ill and require oxygen, while 5% become critically ill and need intensive care. Ageing people with underlying chronic disease are at higher risk of developing serious or critical illness and death. Some healthy adults without known serious chronic illness may be vulnerable to severe complications and or death by covid19. In general, clinical outcomes of COVID-19 varies between individuals from spontaneous viral clearance and severe illness or death specially among elderly people and in less extent in healthy adults.

IL6 is cytokine involved in a variety of host inflammatory reaction produced by numerous types of cells, particularly lymphocytes, and fibroblast and monocytes as well. This diversity to host reaction may be affected by host genetic factors including alteration in gene encoding cytokines as proinflammatory agent. IL 6 gene polymorphism may be implicated in developing serious or critical illness among healthy adults who have been infected with COVID-19.

High level of IL6 and CRP have been related to poor prognosis among those who have been included in this study. Future large studies need to address this issue. Continuation of more research on IL6 gene polymorphism to determine its role in some mortality and pathogenicity among healthy adults infected by COVID-19 in order to get significant knowledge how to reduce mortality rate among such patients.

Introduction

The COVID-19 has raised the concern of the whole world due to its sudden presence and it is causing a health and economic crisis that the international community has not witnessed for decades.

This disease affects different age groups, and the symptoms are being described as mild, moderate and severe forms of symptoms. Younger individuals and children experiencing mild symptoms (1). Several studies have shown asymptomatic infection in significant fraction of some individuals (2). The virus strongly affects the elderly patients and those who have underlying chronic diseases in addition to immune system dysfunction, which resulted in high mortality rate among them (3).

In some cases, the disease causes serious complications and deaths in healthy young and middle-aged individuals who do not have chronic diseases, and this has raised many questions about the causes of these deaths (4). All the processes that take place inside the cell is thought to be governed by genes located at specific locations along the DNA strand inside the nucleus where the two strands of DNA connect with each other to form an X-shaped chromosome.

Each chromosome contains hundreds to thousands of genes which carry the instructions for making proteins. These genes are made of DNA. Genes have the instructions which guide our body how to work and grow, how to face infections and how to develop immunity against microbes. 99.9% of population have the same genetic makeup and 0.1% differences may explain the genetic variation in the causes of some diseases (5).

Genes contain the genetic sequence of amino acids that make up all the proteins in the body, and these proteins are especially important in all metabolic activities inside the cell, and from them the enzymes that are used in the basic functions of the cell are formed, as well as in multiplying of DNA associated with cell division to maintain the viability of the cell. Sets of three nucleotides, known as codons, each correspond to a specific amino acid (6). In order the gene to be polymorphic it requires more than one allele at a specific locus on gene and it must also occur in a population at a rate of at least 1% (7).

Several genes are thought to play a role in causing of Rheumatoid arthritis. the severity of disease can vary depending on polymorphism within genome (8).

Alleles are forms of same gene with small differences in their sequence of DNA bases, which can vary in size from single nucleotide polymorphism and up to several hundred base paired long (9), while mutation is the change in DNA sequence away from normal. It is encoded in human by the IL-6 gene, which is located on chromosome 7 (10). It is a protein belongs to the group of cytokines with both pro and anti-inflammatory properties. The type of response depends on if it is preceding by TNF response or not. When IL-6 is signaling in macrophages it induces pro-inflammatory response, but when it is signaling in muscle is independent of a TNF response and is anti-inflammatory (11).

IL6 is a key mediator of fever and acute phase response which is responsible for stimulating acute phase protein, which explain high level of CRP, as well as neutrophil in the bone marrow and antagonistic to regulatory T cells. When an individual is exposed to infection, the cells of the innate immune system, called antigen presenting cells like macrophages has a key role in the immune response by presenting foreign peptide on HLA 2 molecules and secret cytokines like IL6 which regulate immune and inflammatory response by activating of both B and T lymphocytes as humoral and cellular immunity, induction of acute phase protein synthesis in the liver and modulation of hematopoiesis.

Gene is regulated so that they are expressed when it is needed (12). Depending on its external factor (e.g., Temperature and other stresses) and its internal factors (e.g., cell division cycle, infection status) cell regulates its gene expression. After exposure to the infection, intracellular signaling pathways begin which lead to up regulation of gene expression to tell cell to make a cytokine like IL- 6.

The production of the cytokines is genetically controlled to avoid over or under- production of these necessary components in the immune response. During the virus infection, pro-inflammatory cytokines (e.g., IL6, IL-1, TNF) are produced by the immune system cells, and they work to summon the inflammatory immune system cells to the site of infection, and thus cytokines are important in early infection, without them, the immune system will not be able to respond to the virus because these cytokines regulate the immune and inflammatory response.

When large amounts of cytokines are produced, this will trigger excessive immune response that leads to the infiltration of inflammatory immune system cells into other vital organs of the body such as heart, liver, kidneys and nervous system, which leads to inflammation of these organs with multiple organ dysfunction syndrome.

This is called cytokine storm syndromes (CSS) which can be defined as a condition that causes systemic inflammatory response syndrome by many factor like infection, cancer immunotherapy and certain drug (13), which occur when immune cells activated and release large number of inflammatory cytokines, especially IL-6 in Covid-19, which in turn activate more immune system cells. Genetic variation between populations may take in consideration when we research the possible causes of (CSS). Cytokine storm syndromes and viral overload have been implicated in the severely and poor prognosis illness.

IL-6 disrupt T-regulatory cells, which suppress the T-and B lymphocytes cells when infection subsides to Prevent them to turn into destructive cells. The presence of many forms of the same IL-6 gene (alleles) may causes genetic variation in the pattern of the immune response to covid-19, which explain the difference in the susceptibility to the infection and the severity of symptoms.

Cytokines gene polymorphism may be implicated in uncontrolled production of huge amount of potent proinflammatory cytokines specially IL6 which is associated with poor prognosis outcomes.

This genetic variation can explain why some Healthy, middle-aged patients without underlying chronic diseases are being severely affected by covid-19 with certain mortality rate. Some patients who develop swift severe or critical illness that justify admission to ICU with mechanical ventilation or oxygen therapy may indicate multiorgan dysfunction with poor prognosis.

The genetic factor may play a tangible effect on the pattern of the individual's response mechanism against covid-19. Most of patients who were severely affected by COVID-19, had demonstrated high levels of Pro-inflammatory cytokines especially IL-6, IL-1, IL-2, and TNF - alpha, which indicate cytokines release syndrome (14). Some studies have demonstrated that patients with a certain gene polymorphism in IL-6 appear to be more susceptible to life threatening encephalitis when they infected with enterovirus 71, despite this virus normally causes mild illness called Hand, foot, and mouth disease (15). This link as mentioned above can give us evidence that may explain the pathophysiology of COVID-19 and severity of symptoms and mortality rate in some patients with IL-6 gene polymorphism.

Aging patients and COVID-19

Elderly people with preexisting chronic disease (such as lung disease, cardiac disease, high blood pressure, diabetes, obesity, cancer,) are at higher risk to develop serious or critical illness than other (16).

senescence associated secretory phenotype (SASP) is responsible for many age-related diseases by releasing inflammatory cytokines from these non-divided and highly metabolic active senescence cells (17) and thus, lead to chronic inflammation, induction of fibrosis and inhibition of stem cells (18).

Non-senescent cells can be induced to become senescent by SASP factors (19). Immune system function can be suppressed by chronic inflammation induced by (SASP) senescent which can be one cause aging population are more vulnerable to Covid-19 (20). In the beginning, the SASP act as immunosuppressive (characterized by TGF-beta1) but progresses to be pro-inflammatory (characterized by IL-6 and IL-8) (21) (22).

IL-6 can play a role in developing severe illness for obese patients who get sick by covid-19 which can be attributed to high amount of proinflammatory cytokines such as IL-6 secreted by adipose tissues, and more come from immune cells called macrophages that sweep in to clean up dead and dying fat cell which can explain obesity-related diseases. 10% -35% of IL6 can be secreted by adipose tissues in the absence of inflammation (23).

Corticosteroid therapy can be used as anti-inflammatory agent in the severe or critical Covid-19 cases by blocking the effect of inflammatory mediators and by other hand inducing anti-inflammatory mediator. By direct action on T-lymphocytes corticosteroids exert its effect as immunosuppressive (24). There are many factors determine the therapeutic effect of corticosteroid and other interleukin monoclonal antibody in reducing mortality rate among those who severely affected by covid-19 including:

1. The presence of healthy, active and potent immune system which can fight out coronavirus.
2. presence of any genetic variation predisposition to induce overactive immunity with its immunopathological consequences.
3. The extent of viral load which can be out of body capability to get rid of virus, this can happen at any age group which may also explain certain mortality rate among healthy, middle-aged adults and health care provider who get sick by COVID-19.

Conclusion

IL6 is a cytokine produced by immune cells such as macrophages to mediate and regulate immune response and inflammation against stimulus like viral infection. In normal cases this process is genetically highly regulated as defense mechanism in favor of body, but in some individuals may lead to overactive of immune system by huge amount of proinflammatory cytokines such as IL-6 , leading to serious illness and or death as we see in some healthy, middle- aged adults infected by covid19.

Pro inflammatory cytokines are essential in early infection to regulate and stimulate immune system cells to help host defense mechanisms against any invasion. Sustained high level of these pro-inflammatory cytokines can induce detrimental effect to host defense mechanism by proliferation and maturation of more and more adaptive immune cells, causing systemic inflammation and eventually multi-organ dysfunction with poor prognosis.

IL- 6 gene polymorphism may play a key role in producing higher amounts of this proinflammatory cytokine, leading to systemic hyperinflammatory state, which can explain mortality rate in healthy, middle -aged adults affected by Covid-19 infection. Coronavirus may induce cytokines storm syndromes in some patients, in the absence of gene polymorphism which need more studies to be verified.

Cyclic threshold value can be used to give us picture if patients can develop serious symptoms and helps to make decision about treatment protocol in right time which can play a role in reducing mortality rate in some extent. More studies are needed to evaluate the the role of IL6 gene polymorphism in the severity of symptoms and certain mortality rate among healthy, middle aged adults who infected by COVID-19.

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