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COVID-19 Forum: Transformation of Our World and Mental Health

COVID-19 AND FEAR, WHICH COMES FIRST?

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SUMMARY

Today people have a few unanswered questions in their mind, such as "Do negative emotions will co-survive with the COVID-19 pandemic? Which one is worse? Which one will disappear quicker? Is there any connection between negative emotions and being infected by COVID-19 or the severity of infected individuals' symptoms? How are we supposed to live with COVID-19 and adapt our emotional system to the virus for more than one upcoming year?

These uncertainties could result in massive pressure on people. While there is no clear consensus regarding what establishes psychological stress on an individual, the effect of negative affect and psychological stress on increased susceptibility to disease due to altered immune functions is well established. Here we are going through the possible effect of emotions associated with the present pandemic on COVID-19 course of disease and severity of symptoms.

Key words: *coronavirus – pandemics – fear – emotions - immune system*

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CORONAVIRUS DISEASE 2019 (COVID-19)

The species have been living with viruses since the beginning of existence. It seems that human beings and viruses have been ancient friends together. Interestingly, evidence shows the coevolution of coronaviruses and their natural hosts (e.g., bats) from tens of millions of years ago. Such a long-term relationship has allowed some animal species to evolve strategies to coexist with coronaviruses and vice versa (Wertheim et al. 2013). Besides our close relationship with viruses, recent evidence represents the intimate evolutionary association between virus-derived sequences and various cellular immune pathways (Wertheim et al. 2013). For example, our white blood cells' ability to specifically respond to novel pathogens is probably a contribution of viruses' infection of our fathers in the past human history. Thanks to all benefits of viruses that brought us, however, viruses have evolved to develop mutational and epigenetic mechanisms by which they can alter the host's immune responses to their antigens in order to enhance their survivability and pathogenesis and propagating infection in the host (Adhya & Basu 2010).

Coronavirus disease 2019 (COVID-19), an infectious disease caused by severe acute respiratory syndrome Coronavirus 2 (SARS-CoV2), is proposed to have specific genetic and epigenetic changes making itself more challenging than other viruses against human immune function.

COVID-19, the most recent form of coronaviruses, was first identified in December of 2019 in Wuhan and has since spread globally, resulting in the ongoing 2019-20 Coronavirus pandemic. Being so novel for human beings, most of our immune systems have still never faced COVID-19. While our immune system needs to deploy a certain amount of T cells (CD4 and CD8) and B cells in a normal situation, more inflammatory signals and cytokines are required if the infection persists in the organ. In the case of COVID-19, specialists on the ground report that severe cases do not develop a high viral load but a cytokine storm syndrome resulting in hyper-inflammation in respiratory and other vital systems and consequently fatality. The co-author of the textbook of Cytokine storm syndrome (Cron & Behrens 2019) has claimed recently: "It's not from having a super good immune system. It is from having a subtle defect in the ability of immune system to do its job". Being so new to the researchers, it is still not known when exactly B cells will get SARS-COV2 specific antibodies ready to go and what level of antibodies might provoke a severe and overreacted immune response and cytokine storm. What we know for sure is an immune system dysregulation.

COVID-19 AND ITS RELATED EMOTIONAL STATES

The fast and easy transmission of the virus via droplets produced by coughing, sneezing, or talking of the infected person makes this coronavirus highly contagious and so different from other viruses ever in this regard. With all news through all social media published every hour or even every minute, being anxious or worried or stressed seems normal. It is spreading to every continent, forcing us to live with this virus for perhaps a long time. Thus, many people worldwide are living in fear, not knowing where the virus will show up next or how long it will endure dictating their movements. It seems that fear and anxiety are growing as fast as COVID-19 outbreak (Ahorsu et al. 2020, Al-Qahtani et al. 2020, Šljivo et al. 2020). The researchers are not still certain about when exactly recovered patients stop being contagious and there are still doubts about how long immunity lasts after the disease. Not just fear of being infected by COVID-19, but fear of financial and economic challenges, losing jobs, lack of hospital facilities for other health conditions from one side, and the mental pressure imposed by social isolation from the other side may overwhelm individuals and societies in a pool of negative emotions and feelings.

So, what is the solution? Discovering a specific vaccine or treatment or tool kits for rapid testing seems to be the first and to the point solution for this distressing situation. However, having no vaccines or specific treatment yet, the millions of people who have been infected by COVID-19 and all other members of the human species have to rely on their immune function rather than an exogenous targeted medication. Therefore, discovering more about how our immune function works in a regulated and effective manner will be vital in fighting the pandemic.

EMOTION-IMMUNE FUNCTION CONNECTION

What is the impact of current pandemic-derived stresses and negative emotions on our immune response to COVID-19? It has been documented for decades that stressful life events, negative emotion-responsive hormones such as cortisol affect immune functions, including inflammatory processes, wound healing, responses to infectious agents, and vaccinations (Sapolsky et al. 2000, Kiecolt-Glaser et al. 2002, Seiler et al. 2020). The fact that the central nervous system (CNS), endocrine system, and immune system interact with each other and the impact that emotions have over the sensitive interplay among these systems is now well established in psychoneuroimmunology (PNI) studies.

In the case of any infectious agents such as COVID-19, while acute inflammation run by the immune system is an adaptive response, prolonged and high-intensity inflammatory responses are disadvantageous to health by damaging other vital organs. The potential of exaggerated inflammatory responses triggered by exposure to psychological restraint stress and negative emotions (such as fear and anxiety that we all are experiencing during the current COVID-19 pandemic) has been demonstrated in experimental studies (Bartolomucci et al. 2003, Korte et al. 1992). Besides, chronic stress or negative emotions can suppress or dysregulate innate and adaptive immune responses through a prominent gateway named the endocrine system by changing different cytokine balance types (Dhabhar 2014). For example, it has long been recognized that psychological stress can enhance the susceptibility to influenza and common cold by suppressing the host resistance to infection and consequently increasing the rates of infection (Glaser & Kiecolt-Glaser 2005). Moreover, negative emotions, anxiety, depression, and loneliness have been shown to impact modulating antibody and T cell responses to antiviral vaccinations resulting in suppressed immune responses (Coughlin 2012, O'Connor et al. 2014). Also, in PNI animal model studies, stress causes an apathetic response of T cells in response to a pathogen and a decrease in natural killer cell cytotoxicity (Littrell 2008).

On the other hand, the brain contains a high density of corticosteroid receptors in the prefrontal cortex, hippocampus, and amygdala, and consequently, cortisol could modulate emotional information processing through its action in these areas. In this regard, negative emotions caused by a stressful event such as social isolation or fear of being infected by COVID-19 go through enhanced processing, which could make cognitive emotion regulation more difficult, exacerbating the emotion-endocrine system-immune dysregulation cycle (Roelofs et al. 2007, Tsumura et al. 2015).

It is worth mentioning that substantial literature has demonstrated that not all individuals display immune changes following stressful life events. The level of perceived stress may attribute to the variability among individuals in the magnitude of their immune responses to stress. For example, the perceived demands imposed by the COVID-19 pandemic that exceed the individual's ability to cope, result in psychological stress response composed of negative cognitive and emotional states. In this regard, cognitive emotion regulation mechanisms that try to reappraise social quarantine events by inhibiting negative interpretations could not work properly in a brain full of cortisol and negative affect. These stress responses are thought to influence immune function through neuroendocrine responses (McRae et al. 2013).

Furthermore, there is a body of literature in humans, pointing to predicting psychosocial perceived stresses for reactivation of latent viruses (Seiler et al. 2020). Murdock et al. reported that higher self-reported health

was associated with lower reactivation of latent herpes viruses and inflammation(Murdock et al. 2016). Also, increased antibody titers against Epstein-Barr virus viral antigen (VCA) have been observed in a wide variety of negative emotions raising contexts, including depression (Bennett et al. 2012), perceived stress (Brook et al. 2017), childhood adversity (Fagundes et al. 2013), bereavement or divorce (Derry et al. 2012), exam stress (Matalka et al. 2000), attachment anxiety (Fagundes et al. 2014) and perceived discrimination (Christian 2012).

On the other side of the story, several studies have demonstrated that positive emotional dispositions and their associated hormones such as growth hormone and prolactin have been associated with increased antibody response to the vaccine and boosting many aspects of the immune response (Marsland et al. 2006, Steptoe et al. 2008). For example, investigations represent that growth hormone is lower in depressed patients and chronically distressed caregivers (Krogh et al. 2010). In a meta-analysis of 34 studies, the positive effects of mind-body therapies such as Tai Chi, Qi Gong, meditation, and Yoga on the immune system and virus-specific antibody responses to vaccines have been represented (Morgan et al. 2014). Positive emotions may act as a buffer of stress responses, reduce negative appraisals of events, and facilitate adaptive coping (Bostock et al. 2011).

However, another reverse pathway may exist, which connects the emotions to the immune system function. Several cytokines and inflammatory mediators are contributable to the COVID-19 pathophysiology and severity. Interleukin-1b (IL-1β), IL-2, IL-6, IL-10, and Tumor Necrosis Factor-α (TNF-α) have associations with disease severity (Henderson et al. 2020, Pedersen & Ho 2020). Interleukin-1 (IL-1) has a role in the pathophysiology of COVID-19 and the related cytokine storm (Cavalli et al. 2020). It has been shown that increased levels of IL-1β can lead to anxiety in mice (McKim et al. 2018, Wohleb et al. 2014). A high-fat diet is shown to increase the IL-1β, IL-6, and TNF-α levels in the brain, which may lead to anxiety. Blockage of P2X7 receptors, which have a rule in the production of IL-1β, alleviates anxiety symptoms (Dutheil et al. 2016).

Similarly, blockage of TNF-α leads to improvement in anxiety symptoms in obese mice(Fourrier et al. 2019). There may be similar pathways in the human brain, too, in which inflammatory mediators play roles in psychological issues' pathophysiology. Considering these facts, increased levels of these inflammatory mediators in COVID-19 patients can be a potential reason for anxiety, fear, and other psychological issues. There may even be a loop. COVID-19 leads to increases in the production and release of inflammatory mediators, leading to psychological issues. In turn, psychological issues by themselves can lead to further dysregulation of the immune system. In this way, psychological issues and the immune system response reinforce each other, leading to more severe types of diseases and more severe psychological issues.

PITFALLS: POSITIVE EFFECTS OF FEAR AND FEAR IN THOSE WITH UNDERLYING DISEASES; EUSTRESS VERSUS DISTRESS

What does fear or anxiety mean? Both somehow relate to the recognition of a known or unknown expected threat. So, is being afraid or worried about a threat a bad thing? Are we supposed to ignore the message or alarm signaled by fear or anxiety?

From the evolutionary point of view, both fear and anxiety have evolved in mammals to respond to danger to ensure survival. Therefore, some degree of fear or anxiety, or stress is not necessarily bad or considered an immune system-interrupting emotion. Accordingly, we can find terms such as effective or good stress in the psychological literature, a concept that has been named "eustress" by endocrinologist Hans Selye. According to evidence, eustress, which keeps the person motivated and aroused about life, can be considered an effective warning sign that brings awareness to the person's current situation to provide necessary changes and solutions for the potential threats.

While chronic stress and high levels of perceived stress that disrupt the person's ability to cope with the situation (i.e., distress), may lead to anxiety, withdrawal, and depressive behavior, eustress enhances one's functioning. It can be beneficial for recruiting strategies to improve our overall mental and physical well-being. At the physical level in the body, the differentiation between eustress and distress depends on the person's perception of the stress and way of adapting to the primary stressor that caused it. In other words, the body cannot physically distinguish between eustress or distress. However, the intensity of arousal caused by stressors should be considered an essential factor in discerning effective vs. disruptive stress. The Yerkes-Dodson model depicts the optimum balance of stress with a bell curve (Quick et al. 1997). This model is supported by evidence demonstrating that behavioral and emotional coping strategies are related to perceived stress changes.

So, it seems that some degree of stress, fear, or anxiety may have some silver linings, protecting us against harm and threats. Interestingly, one can hypothesize the effect of eustress on following sanitation protocols and obeying rules regarding wearing a mask and practicing good hygiene to decrease COVID-19 incidence and mortality in societies. However, after being infected by the virus, being afraid, worried, and overwhelming with other negative emotions can decrease the immune system's efficacy in interacting with the virus.

MAIN QUESTIONS

According to our approach toward PNI, questions can arise about the association between COVID-19 incidence and emotions associated with COVID-19 outbreak. Finding practical answers for the possible connection between negative emotions induced by COVID-19 and being infected by COVID-19 or the severity of the symptoms in infectious individuals seems necessary soon.

It seems that emotions and our feelings toward the COVID-19 pandemic can act as a double-edged sword. Some levels of anxiety and fear are needed in order to motivate people to protect themselves against COVID-19. On the other hand, high levels of anxiety and fear can act completely reverse and lead to dysregulation in the immune system function and put people at the risk of severe disease types. How can these emotions be controlled to have benefits from them? Where is the border between beneficial and harmful emotions?

Whatever cause, clinicians and researchers are supposed to present possible solutions or scenarios for a new normal life. One can propose cognitive or simply behavioral strategies to ameliorate negative emotions and enhance positive affect throughout the societies to decrease viral load and boost our immune systems against this virus. Is it worth trying?

Studies are reporting the efficacy of cognitive-behavioral-stress management, perceived social support, and coping skills in individuals with HIV+ (the deadliest virus of all) in comparison to drugs alone in enhancing immune function (Antoni et al. 2002), in decreasing cortisol levels (Antoni et al. 2000) and in decreasing viral load (Antoni et al. 2006, Wilson et al. 2017).

Moreover, allowing individuals with HIV+ to write their emotional experiences has been shown to increase CD4+ counts and decrease viral load relative to controls (Petrie et al. 2004). Also, talk therapy based interventions have been shown to decrease viral load in viral diseases (Littrell 2008). An 8-week course in mindfulness meditation boosted antibody levels after influenza vaccination relative to controls (Davidson et al. 2003).

Fear and anxiety are spreading alongside COVID-19, and we are supposed to rely on these strategies against the COVID-19 pandemic. Evidence is depicting the co-surviving of some negative emotions with a crisis even after the crisis ends. So, the proposal that negative emotions will co-survive with the COVID-19 pandemic is not unlikely. Let us ask a better question: which one is worse? Which one will disappear quicker? Chronic negative emotions or COVID-19? We might have to live with COVID-19 and adapt our emotional system with the virus for more than one upcoming year. According to psychological evidence, fully perceiving and understanding emotions and not resisting them are of particular importance in mental and physical health. How we experience the emotions (subjective component), how our bodies react to the emotions (physiological component), and how we behave in response to the emotions (expressive component) are three important parts of emotion perception, either positive or negative. However, appreciating all the negative or positive emotions a person experiences during a day may be difficult without appropriate education.

How are we supposed to inform policymakers to run suitable programs and campaigns to live effectively with the emotions imposed by COVID-19?

CONCLUSION

It seems that COVID-19 and psychological issues affect each other in different ways, and providing novel strategies to educate individuals on how to have a balanced and well mind in response to the COVID-19 pandemic is necessary to have a well immune and endocrine function, which require multi-disciplinary approach psychology, psychiatry, neuroscience, and immunology.

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