COVID-19: adrenal response and molecular mimicry

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TO THE EDITOR,

The host immune response to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) appears to play a critical role in the disease pathogenesis and clinical manifestations. SARS-CoV-2 not only activates antiviral immune responses but can also cause excessive systemic action of pro-inflammatory mediators including cytokine release in patients with severe coronavirus disease-2019 (COVID-19) accompanied by lymphopenia, lymphocyte dysfunction as well as granulocyte and monocyte abnormalities. These SARS-CoV-2-induced immune abnormalities may result in the development of complicating infections by other microorganisms with subsequent severe multiple organ hypoperfusion, hypoxia, and dysfunction, leading to hemodynamic shock and sometimes causing death.

Increasing evidence accumulated from the past year suggests a strong correlation between the COVID-19 infection and autoimmunity. The reported inflammatory/autoimmune-related symptoms by patients, the appearance of circulating autoantibodies, and the diagnosis of defined diverse autoimmune diseases in a subgroup of SARS-CoV-2-infected patients (including those with long-COVID syndrome) indicate the critical and pivotal effect of SARS-CoV-2 virus on human immunity and its capability to trigger autoimmune disorders in genetically predisposed subjects.

The onset of autoimmune diseases may be generated by a variety of factors through the creation of immune system hyperstimulation, which is the case for acute COVID-19. Another possible mechanism of the autoimmune phenomena in COVID-19 is molecular mimicry [1].

In our opinion, one important example of molecular mimicry in the case of COVID-19 is related to the key hormonal system of stress management: the hypothalamic-pituitary-adrenal axis.

Stress responses have counter-inflammatory and shock-protective effects as the adrenal hormones support the barrier function of inflammatory foci and prevent the excessive systemic action of proinflammatory local bioregulators, which are highly relevant in COVID-19-induced hyperinflammatory state and hemodynamic shock. In lungs, glucocorticoids increase the potential of surfactant system response preventing respiratory distress. Direct viral as well as indirect immune-mediated adrenal involvement in COVID-19 may jeopardize these compensatory mechanisms. Blockage of adrenal-mediated stress related counter-inflammatory response may facilitate excessive systemic action of proinflammatory autacoids including cytokine storm in such individuals [Figure 1].

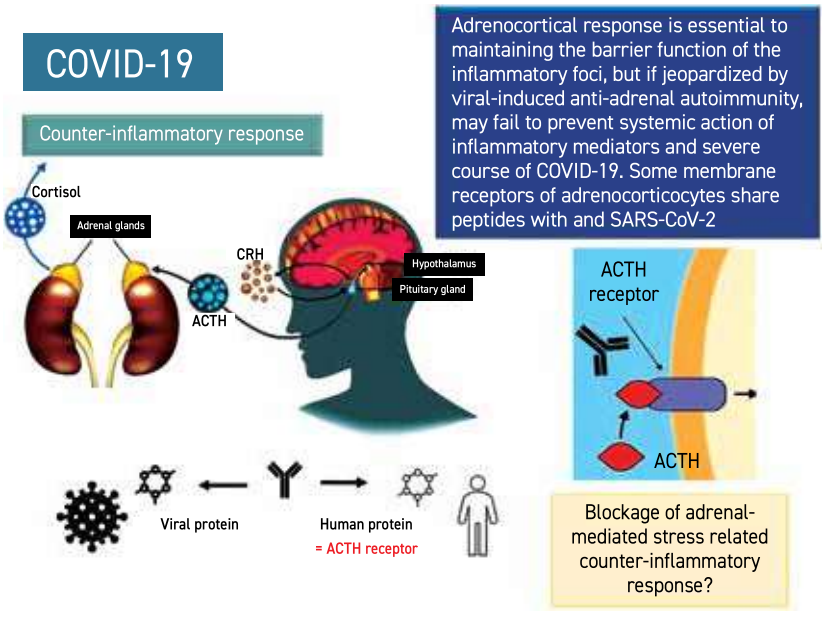
During previous epidemics of coronavirus infection (SARS in 2005) it was shown that in 40% of cases those patients who experienced severe SARS presented with evidence of central hypocortisolism. Hypothalamus and pituitary both express angiotensin-converting enzyme 2 (ACE2) receptors for coronavirus entrance were involved in alteration according to autopsy data of some SARS/MERS victims. The SARS virus was located in adrenals [2].

Moreover, in 2004 Wheatland [3] suspected the existence of homologies between adrenocorticotropic hormones (ACTH) in various mammals and SARS coronavirus replicase 1AB protein, as well as between ACTH and influenza virus peptides. They hypothesized that this connection may cause anti-ACTH autoimmunity in both SARS and influenza.

Corresponding to the assumption of autoimmune reaction against adrenal glands induced by SARS-CoV-2 infection, lymphocytic infiltration of adrenal glands was recently revealed in the patients who tested positive for COVID-19 [4].

Figure 1. A hypothesis on the relationship between severe course of COVID-19 and anti-adrenocortical autoimmunity and adrenocorticotropic hormone

ACTH = adrenocorticotropic hormone, COVID-19 = coronavirus disease-2019, SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2



It is well known that angiotensin II is a key regulator of adrenal cortex glomerular zone and that adrenocorticocytes possess receptor for angiotensin II. ACE 2 receptors (used by SARS-CoV2 as an entrance gate into the affected cells) are also expressed in the adrenal cortex. At the same time, hypocortisolism is revealed in severe SARS-CoV-2. Glucocorticoid treatment appeared to be effective in such cases [5].

Based on these findings, we can assume that autoantibodies against adrenocortical receptors/bioregulators may be elicited in COVID-19 via the idiotype-anti-idiotypic mechanism as anti-idiotypes against those antiviral antibodies aimed at viral sequences are essential for intracellular penetration of SARS-CoV2. A similar mechanism in 1983, long before current pandemic, was postulated by Paul Plotz for autoimmunity induced by viral infections and confirmed for some viruses.

If this hypothesis is true for SARS-CoV2, it means that such auto-anti-idiotypes may alter adrenals. SARS-CoV2 epitopes are known to share multiple peptides with human proteome.

Based on this data, we performed a bioinformatic analysis of probable peptide sharing between human adrenal autoantigens and coronavirus peptides. Experimentally validated epitopes cataloged in the Immune Epitope Database (IEDB) and present in SARS-CoV-2 or in control human coronavirus 229E were analyzed for peptide sharing with the following human proteins:

- ACTHR (ACTH receptor)
- Angiotensin II receptor Type-1
- Angiotensin II receptor Type-2
- Pro-opiomelanocortin (precursor of ACTH and several other pituitary hormones)
- ACTH [Figure 2]

Figure 2. Bioinformatic analysis of pentapeptide sharing between human antigens and antigens of coronaviruses. Shared pentapeptides are highlighted in purple

1. Q01718|ACTHR **Adrenocorticotropic hormone receptor**

Organism	Peptides Matched
Human coronavirus 229E	-
SARS-CoV-2	ETTAD, IVGVL, LLAVF

2. P30556|AGTR1 **Type-1 angiotensin II receptor**

Organism	Peptides Matched
Human coronavirus 229E	FVVGI, SLPAI, SQNST
SARS-CoV-2	-

3. P50052|AGTR2 **Type-2 angiotensin II receptor**

Organism	Peptides Matched
Human coronavirus 229E	DKHLD, KVFGS
SARS-CoV-2	IFYIT, TCYFG, VIGFL

4. P01189|COLI **Pro-opiomelanocortin**

Organism	Peptides Matched
Human coronavirus 229E	LLALL, LLLAL
SARS-CoV-2	LALLL, LLLAL, LLVAA

5. P01189|138-176 **ACTH or Corticotropin or Adrenocorticotropic hormone**

NO MATCHES

Thus, human angiotensin II receptor type 2 as well as human proopiomelanocortin share peptides with both of the coronoviruses we checked. Angiotensin II receptor type 1 shares peptides only with coronovirus 229E. Human ACTH receptors share peptides with SARS-CoV2 only. ACTH fragments of proopiomelanocortin do not match with coronavirus peptides. The results are in accordance with our assumptions based on indirect adrenocortical involvement.

It is worth analyzing autoantibodies toward adrenal antigens in COVID-19 of various severity and outcomes, including long COVID syndrome. So far such data are absent, although several cases of newly onset peripheral or central adrenal insufficiency during and after COVID-19 have been reported.

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Every time I see an adult on a bicycle, I no longer despair for the future of the human race.
H.G. Wells (1866–1946), English writer

What power has love but forgiveness?
William Carlos Williams (1883–1963), American poet, writer, and physician