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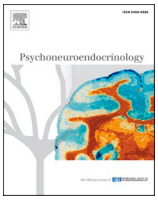

# What to do now that hypocortisol appears to be a predominant sign of long COVID?

An infection with the SARS CoV-2 pathogen leads to a series of health and psychological long-term consequences, called Long COVID (LC). LC massively impairs the quality of life and performance of those affected for months and -probably- many years. While apparently the probability of occurrence varies among virus variants (delta > omicron), the exact biological mechanisms leading to LC remain obscure.

However, results from a recently presented study that has not yet been quality-assured by peer review may shed new light on the connection. The "Mount Sinai-Yale Long COVID (MY-LC)" study team reported in their medRxiv preprint that a strikingly low cortisol level in LC sufferers was the most significant predictor for the presence of LC (Klein et al., 2022). Literally hundreds of immunological and serological parameters had been analyzed in the 215 individuals studied (with and without LC) and evaluated using machine learning approaches and other methods. Although several other biological abnormalities also distinguished LC sufferers from comparison subjects, the observed hypocortisolism of the LC group was the most statistically significant distinguishing feature. Accordingly, the cortisol levels of LC sufferers were only about 50% of the hormone levels of healthy subjects! Interestingly, ACTH levels were unremarkable.

This finding is both confusing and electrifying. Can it be true that a low basal glucocorticoid level is indicative or even responsible for the multitude of symptoms described in LC? Certainly, hypocortisolism, if it actually exists in LC, does not have a particularly high specificity for LC and does not appear to be very helpful in making a diagnosis. In numerous disorders such as PTSD, chronic fatigue syndrome, fibromyalgia, rheumatoid arthritis, asthma and others, the adrenal cortex also produces significantly less cortisol (Heim et al., 2000). And yet it seems bio-logical that too little cortisol could promote the development and maintenance of LC. As the most important endogenous immunosuppressant in humans, cortisol helps to keep inflammatory processes under control. Cytokine-induced wildfires in the brain and peripheral organs are candidate consequences of chronically low cortisol levels. Therefore, the observation made by Klein and colleagues fits well into the picture, as chronic inflammatory processes obviously condition the cardinal symptoms of LC.

Does this explain the biological process of LC development? Not at all. First, despite all enthusiasm for the published finding, the methodology of the MY-LC study has to be looked at critically. Cortisol levels were determined from blood samples that had been drawn at different times of the day. Certainly, the authors report having statistically 'controlled' for a possible influence of the time of measurement. However, with group sizes of 15 and 25 in the control groups, the null hypothesis ("The time of day at which the blood sample was drawn has no effect on group differences.") can only be rejected with a high degree of uncertainty. In addition, quite little valid information about adrenocortical activity can be derived from a spot blood sample.

Therefore, the observation of a possible hypocortisolism in LC is electrifying. Now we are called to work with better methods and much larger sample sizes to put the main result of the MY-LC study to the test. Presumably, the use of cortisol determinations in hair will allow for really interesting observations that would remain hidden with other methods. Hair samples tell us quite a bit about an individual's 'endocrine history' - after all, we can use them to look retrospectively at how much or little of a hormone had been produced well before the sample collection date. Did the individuals later affected by LC tend to underproduce cortisol even before infection with SARS-CoV-2? Or does it hit particularly hard those in whom the virus attacks the adrenal cortices causing hypocortisolism? Indeed, initial data are available showing that SARS-CoV-2 attacks the adrenal cortices and can lead to (temporary?) insufficiency of the gland (Kanczkowski et al., 2022).

At the time writing this commentary, I approached the members of a support group for LC sufferers and asked for donations of hair samples for a quick look at the intriguing possibility that a SARS-CoV-2 infection could really *induce* a hypocortisolism. Within a few hours a participant of the Dresden Burnout Study (Penz et al., 2018) replied in an email that her hair cortisol levels were puzzling: While her hair cortisol levels had been a normal 5.25 pg/mg before COVID, the levels had dropped to an alarming 0.64 pg/mg 10 months after her infection!!.

If the finding of Klein et al. (2022) and the single LC case observation are confirmed, this would possibly have important consequences for psychoneuroendocrinological studies as well. Then, in our studies in the future, we would have to ascertain exactly who among our study participants exhibited altered HPA activity and reactivity as a consequence of SARS-CoV-2 infection. Intervention studies will probably mushroom. Can we prevent or alleviate LC symptoms such as fatigue, brain fog, or (working) memory problems with low-dose steroidal and nonsteroidal anti-inflammatory drugs? With LC prevalence conservatively estimated to be 1%− 5%, the psychoneuroendocrinological dimensions of LC are becoming a significant area of future research, not least because of the tremendously large number of people affected worldwide. Let's hope that our funders will be electrified, too!.

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