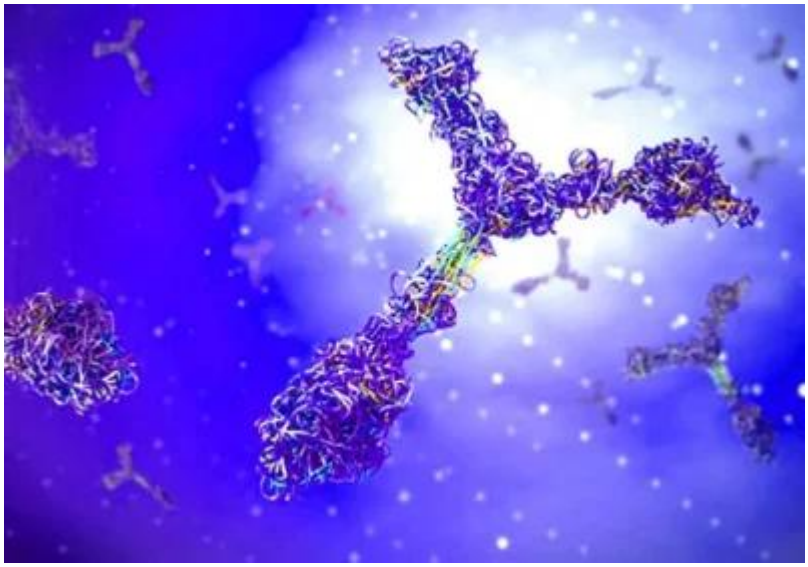
The most commonly reported symptoms of post-COVID-19 vaccination syndrome (PCVS) are malaise, chronic fatigue, cardiovascular disorders (orthostatic intolerance, tachycardia, palpitations), peripheral neuropathy (dysesthesia, hypesthesia), muscular disorders (myalgia, weakness), gastrointestinal disorders (nausea, weight changes) and cognitive disorders. The presentations of PCVS overlap with various multisystemic dysautonomia syndromes such as myalgia encephalomyelitis/chronic fatigue syndrome (ME/CFS), postural orthostatic tachycardia syndrome (POTS), fibromyalgia/chronic pain syndrome, small fiber neuropathy (SFN), and mast cell activation syndrome (MCAS). As previous studies have shown the correlation between autoimmune response against receptors and transmitters involved in autonomic regulation and the incidence, duration, and severity of ME/CFS or POTS, the researchers from Germany in this study investigated the concentrations of autoantibodies against receptors involved in autonomic regulation in individuals who developed PCVS. The researchers pointed to many unreported PCVS cases due to a lack of diagnostic criteria and the fact that PCVS existence is not generally accepted.

Interestingly, in 2021, Yapici-Eser et al. hypothesized that mimicry between human proteins and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) proteins may have a role in neurobiological pathways that underlie the neuropsychiatric manifestations of COVID-19 and long COVID syndrome. They utilized a computational methodology (Host-Microbe Interaction PREDiction Algorithm) to detect mimicry between human proteins and SARS-CoV-2 proteins and classified these interactions according to the molecular paths of COVID-19-associated neuropsychiatric symptoms. The results showed that SARS-CoV-2 proteins mimic 12 proteins linked with the muscarinic acetylcholine receptor 1 and 3 signaling pathway, 12 proteins linked with the muscarinic acetylcholine receptor 2 and 4 signaling pathway, 9 proteins linked with the beta1 adrenergic receptor signaling pathway, 9 proteins linked with the beta2 adrenergic receptor signaling pathway, 6 proteins linked with the beta3 adrenergic receptor signaling pathway, 5 proteins linked with the alpha-adrenergic receptor signaling pathway, and 16 proteins linked with the endothelin signaling pathway. Also, the SARS-CoV-2 spike protein has been found to mimic numerous human proteins, including angiotensin-converting enzyme 2. (Yapici-Eser et al. Neuropsychiatric Symptoms of COVID-19 Explained by SARS-CoV-2 Proteins' Mimicry of Human Protein. Front Hum Neurosci 2021 15:656313.)
https://www.frontiersin.org/journals/human-neuroscience/articles/10.3389/fnhum.2021.656313/full

Additionally, a recent study on patients who developed new-onset small fiber neuropathy after COVID-19 demonstrated that some of them experienced post-exercise malaise,

neurovascular dysregulation, and dysautonomia consistent with ME/CFS.
https://discovermednews.com/dysautonomia-and-neuropathy-in-small-fiber-neuropathy-after-covid-19/



About the study

The study included participants who developed PCVS after the mRNA COVID-19 vaccination and healthy vaccinated individuals. Exclusion criteria were: the occurrence of symptoms after receiving other vaccines (including non-mRNA COVID-19 vaccines) or after acute COVID-19, a history of ME/CFS, POTS, or other potentially significant disease or syndrome, and adverse reactions lasting more than two weeks after full vaccination.

Pfizer/BioNTech vaccines received 159 individuals who developed PCVS and Moderna vaccines 32 individuals with PCVS. 47 PCVS cases were vaccinated with one dose, 96 PCVS cases with two doses, and 48 PCVS cases with three doses of Spikevax, Moderna/Comirnaty, or Pfizer/BioNTech mRNA COVID-19 vaccines. In 17 PCVS cases, one vaccination with a vector-based vaccine preceded the mRNA vaccination. Healthy controls were vaccinated with two doses of Spikevax or Moderna vaccines. The vaccination response in all participants was confirmed by sero-reactivity against the S1 subunit of the severe acute

respiratory syndrome coronavirus 2 (SARS-CoV-2) spike (S) protein.

Paired serum samples were taken 48 hours before the first vaccination and six months after the second vaccination. Antibodies against angiotensin II type 1 receptor, angiotensin-converting enzyme 2, endothelin-1 type A receptor, the group of adrenergic receptors, such as alpha-1 adrenergic receptor (α1-adr-R), alpha-2A adrenergic receptor (α2a-adr-R), alpha-2B adrenergic receptor (α2b-adr-R), alpha-2C adrenergic receptor (α2c-adr-R), beta-1 adrenergic receptor (β1-adr-R), and beta-2 adrenergic receptor (β2-adr-R), the group of muscarinic acetylcholine receptors M1–M5 (M1R–M5R), MAS1 receptor and interleukin (IL)-1 receptor were assessed by immunoassay.

Results

The study enrolled 280 participants, 191 of whom developed PCVS after the mRNA COVID-19 vaccination, and 89 were healthy vaccinated controls. Most participants in both groups were women, 159/191 in the PCVS group, and 71/89 in the healthy control group. The mean age of PCVS participants was 40 years and healthy controls was 39 years.

The concentrations of autoantibodies against receptors involved in autonomic regulation before and after vaccination

The concentrations of almost all potentially relevant autoantibodies differed significantly in both groups before and after vaccination.

In vaccinated healthy controls, a cluster of autoantibodies targeting the renin-angiotensin-aldosterone system and other components of cardiovascular regulation decreased after vaccination compared to pre-vaccination levels. A decrease of 25-50% was found for autoantibodies against angiotensin II type 1 receptor, endothelin-1 type A receptor, the group of muscarinic acetylcholine receptors (M1R, M2R, M3R, M5R) the group of adrenergic receptors (α1-adr-R, α2a-adr-R, β1-adr-R, β2-adr-R) and MAS1 receptor.

Concentrations of autoantibodies against the IL-1 receptor, and the adrenergic receptor α2b-adr-R, involved in thrombogenesis, decreased in participants suffering from PCVST and increased (in a median of 15–25%) in vaccinated healthy controls after vaccination.

As the observed effect of COVID-19 vaccination on the levels of autoantibodies against receptors involved in autonomic regulation was more extensive in healthy vaccinated individuals than in participants who developed PCVS, the authors speculated that these

findings probably represent a physiological response to mRNA vaccination.

Comparison between individuals with post-COVID-19 vaccination syndrome and vaccinated healthy subjects

The concentrations of autoantibodies against 8 of 16 receptors differed significantly between individuals with PCVS and healthy controls. Individuals with PCVS had higher levels of autoantibodies against six receptors, including the angiotensin II type 1 receptor, endothelin-1 type A receptor, M2 and M3 muscarinic acetylcholine receptors, β2 adrenergic receptor, and MAS1 receptor than healthy controls, and *vice versa*, the same autoantibodies were decreased in healthy controls compared to participants who developed PCVS. Interestingly, all of these proteins were detected in the above-mentioned study on mimicry between human proteins and SARS-CoV-2 proteins.

The authors also compared levels of total immunoglobulin-G, the cardiac markers (pro-B-type natriuretic peptide, troponin), and inflammation markers interleukin (IL)-6, IL-8, and C-reactive protein between individuals with PCVS and healthy vaccinated controls. Only IL-6 and IL-8 were identified as potential discriminative biomarkers of PCVS. The levels of IL-6 and IL-8 were higher in most subjects with PCVS than in healthy vaccinated controls. It is worth noting that patients diagnosed with ME/CFS were found to have increased IL-6 levels correlating with an even greater increase in IL-8.

Conclusion

This study detected differences in autoantibodies against receptors involved in autonomic regulation between individuals diagnosed with post-COVID-19 vaccination syndrome and vaccinated healthy individuals. The authors suggested that these results could be important for understanding PCVS and the associated dysautonomia.

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Journal Reference

Semmler A, Mundorf AK, Kuechler AS et al. Chronic Fatigue and Dysautonomia Following COVID-19 Vaccination Is Distinguished from Normal Vaccination Response by Altered Blood Markers. Vaccines 2023 *11*(11), 1642. https://doi.org/10.3390/vaccines11111642