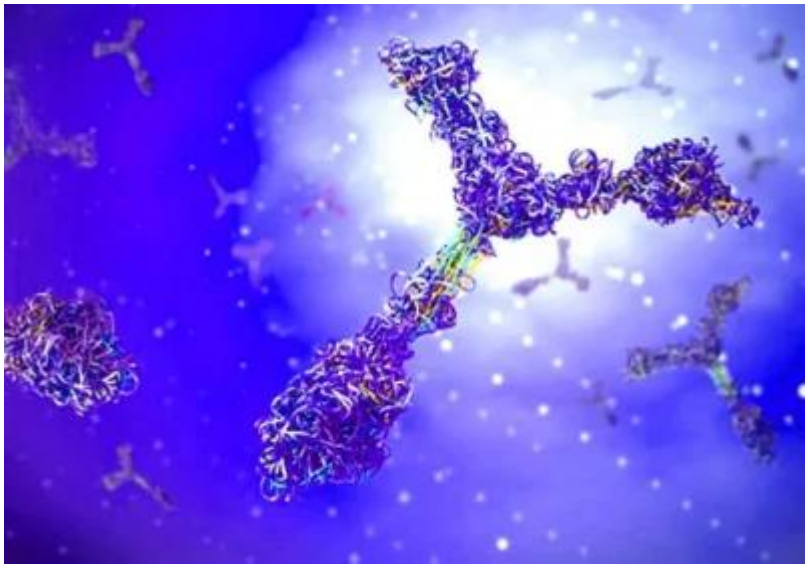
In both messenger RNA (mRNA)-based vaccines, BNT162b2 (Pfizer- BioNTech) and mRNA 1273 (Moderna), a mRNA sequence determines the structure and assembly of the immunogen, the SARS-CoV-2 spike (S) glycoprotein. The post-COVID-19 vaccination syndrome (PCVS) symptoms start shortly after the COVID-19 vaccination. The most commonly reported are malaise, chronic fatigue, cardiovascular disorders (orthostatic intolerance, tachycardia, palpitations), peripheral neuropathy (dysesthesia, hypesthesia), cognitive dysfunction, muscular disorders (myalgia, weakness, fibrillations), and gastrointestinal disorders (nausea, weight changes). In this study, the researchers from Germany investigated how COVID-19 vaccination affects the concentrations of autoantibodies against receptors involved in autonomic regulation in individuals with PCVS. The researchers pointed to a high number of unreported cases of PCVS due to a lack of diagnostic criteria. Furthermore, it is not generally accepted that PCVS exists.

The presentations of PCVS overlap with various multisystemic dysautonomia syndromes such as myalgic 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). 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.

There are also overlapping presentations between ME/CFS or SFN with long COVID syndrome. A recent study conducted in patients who developed new-onset SFN after a documented 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 280 participants, 191 developed PCVS after mRNA COVID-19 vaccination, and 89 healthy vaccinated controls. The majority of participants in both groups were women, in the group of participants with PCVS 159 of 191, and in the group of healthy controls 71 of 89. The mean age was 40 for PCVS participants and 39 years for healthy controls.

Participants who developed PCVS were vaccinated with one (47 cases), two (96 cases), or three doses (48 cases) of mRNA Spikevax, Moderna or Comirnaty, and Pfizer/BioNTech vaccines. Pfizer/BioNTech vaccines received 159 cases and Moderna vaccines 32 cases. In 17 cases, the mRNA vaccination was preceded by one vaccination with a vector-based vaccine. Healthy controls were vaccinated with two doses of Spikevax and Moderna vaccines. The vaccination response in all participants was confirmed by sero-reactivity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike S1 protein. 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 to vaccination lasting more than two weeks after full vaccination.

Paired serum samples were taken 48 hours before the first vaccination and six months after the second vaccination. Immunoassay was used to evaluate 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), MAS 1 receptor and interleukin-1 receptor.

Results

In both groups, the concentrations of almost all potentially relevant autoantibodies differed significantly before and after vaccination. Interestingly, the results were more extensive in the group of healthy vaccinated controls than in participants diagnosed with PCVS.

In healthy vaccinated controls, a cluster of antibodies 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 MAS 1 receptor.

Importantly, healthy vaccinated controls had increased concentrations (in median 15–25%) of autoantibodies against interleukin-1 receptor, and adrenergic receptor α2b-adr-R, involved in thrombogenesis. In contrast, participants with PCVST had significantly decreased levels of autoantibodies against interleukin-1 receptor and adrenergic receptor α2b-adr-R after vaccination.

Since the effect of COVID-19 vaccination on the levels of autoantibodies against receptors involved in autonomic regulation was much more extensive in healthy individuals than in participants who developed PCVS, the authors speculated that these findings probably represent a physiological response to mRNA vaccination.

Comparison between the two groups revealed that concentrations of autoantibodies against eight of the 16 receptors differed significantly between individuals with PCVS and healthy controls. The levels of autoantibodies against six receptors, angiotensin II type 1 receptor, endothelin-1 type A receptor, two muscarinic acetylcholine receptors M2R and M3R, adrenergic receptor β2-adr-R, and MAS 1 receptor were higher in individuals with PCVS compared to healthy controls, and *vice versa*, the same autoantibodies were decreased in

healthy controls compared to participants who developed PCVS.

The authors also examined whether concentrations of several biomarkers could distinguish individuals with PCVS from healthy vaccinated controls, such as total immunoglobulin-G, SARS-CoV-2 serology, cardiac markers (pro-B-type natriuretic peptide, troponin), and inflammation markers interleukin (IL)-6, IL-8 and C-reactive protein. 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. Notably, an increase in IL-6, which correlated with an even greater increase in IL-8, was also observed in patients diagnosed with post-COVID syndrome or ME/CFS.

Conclusion

This study has shown that autoantibodies against two receptors, angiotensin II type 1 receptor and alpha-2B adrenergic receptor, and serum levels of IL-6 and IL-8 distinguished individuals who developed post-COVID-19 vaccination syndrome from healthy vaccinated individuals.

The authors suggested that PCVS is distinct from various acute autoimmune phenomena reported in the context of COVID-19 vaccination, and therefore, these findings may be important for understanding PCVS and associated dysautonomia.

This article was published in Vaccines.

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