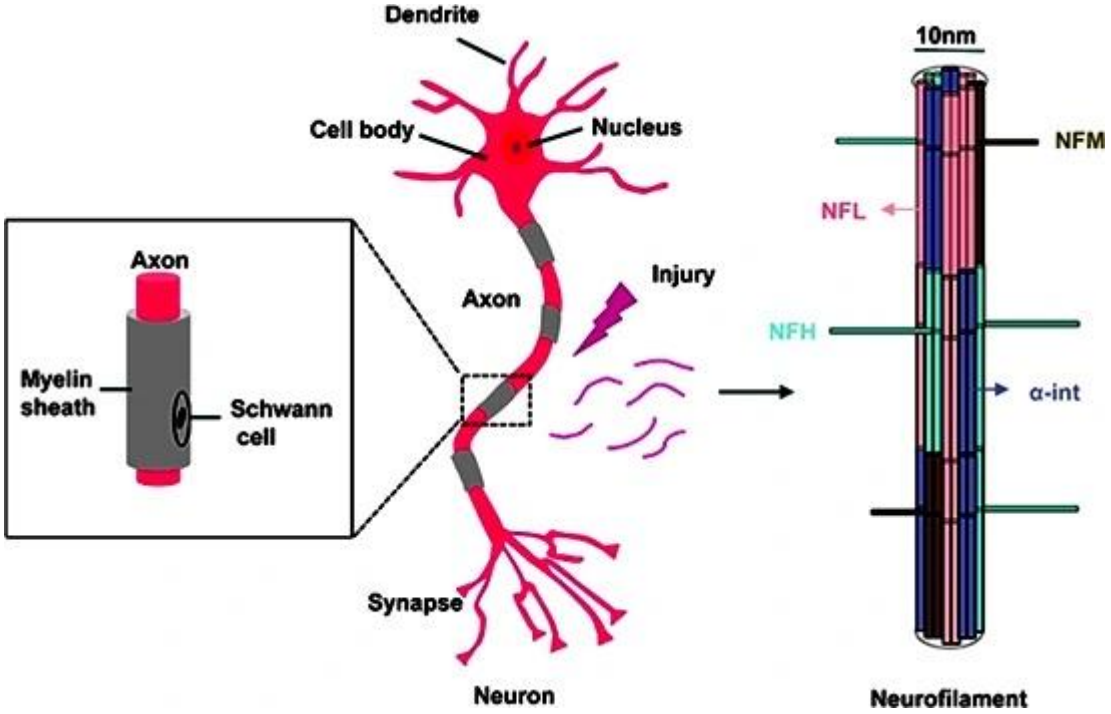
There are numerous persistent symptoms following the COVID-19 vaccination, referred to as the post-COVID-19 vaccination syndrome (PCVS). Due to the inadequate definition of the syndrome and the lack of specific diagnostic criteria or biomarkers, PCVS diagnosis remains difficult to distinguish from other diseases. New-onset autoimmune phenomena with pathologic autoreactive antibodies were found to be associated with PCVS, such as immune thrombotic thrombocytopenia, autoimmune liver diseases, IgA nephropathy, rheumatoid arthritis, and systemic lupus erythematosus. In this study, the authors from Germany investigated the frequency and epitopes of autoantibodies against peripheral nerve structures in patients diagnosed with post-COVID-19 vaccination syndrome.

Recent studies have identified a new autoantibody targeting a nuclear antigen, called anti-dense fine speckled 70 (DFS70), and characterized by the fine-granular fluorescence of the nuclei in the interphase and the metaphase chromatin. It was named DFS70 because it causes autoantibody reactivity with a 70 kD protein in the Western blot. Protein sequence analysis demonstrated that this antigen is identical to lens epithelium-derived growth factor (LEDGF), also known as DNA-binding transcription coactivator p75. DFS70/LEDGFp75 protein is commonly present in mammalian cells and, as a multifunctional stress response protein, is associated with organ-specific autoimmune diseases, allergic diseases, malignancy, and some inflammatory conditions. (Duran AC, et al. The clinical significance of anti-DFS70 autoantibodies and its correlation with Vitamin D levels. North Clin Istanb 2022;9(6):581–589)

Neurofilament proteins (NF) are components of the axonal cytoskeleton, expressed exclusively in neurons. According to molecular weight, there are three NF subunits, NF-H (heavy), NF-M (medium), and NF-L (light), with the light unit of the neurofilament protein (NFL) being the primary component of the neurofilament core. NF proteins in the blood and cerebrospinal fluid are markers of axonal injury due to normal aging or disease processes in the central and peripheral nervous system, including inflammatory, autoimmune, vascular, and traumatic processes. Peripherin (PRPH) is a 57kD type III intermediate filament that is a specific marker for peripheral neurons, including enteric ganglion cells.



About the study

The study included outpatients with peripheral neurological symptoms that developed after COVID-19 vaccination, as well as healthy vaccinated control subjects. Inclusion criteria were receipt of at least one anti-COVID-19 vaccination and the development of new symptoms within 1 month after vaccination. Exclusion criteria were confirmed SARS-CoV-2 infection before the onset of symptoms or another disease diagnosed after the onset of new symptoms. Clinical assessment included electrophysiological examination and skin biopsy in patients complaining of paresthesia and neuropathic pain. Laboratory workup followed the guidelines of the German Neurological Society for the diagnosis of polyneuropathy.

Serum IgG autoreactivity was assessed by indirect tissue-based immunofluorescence on sciatic nerves from wild-type mice. Autoantibodies against gangliosides were analyzed in ganglioside blots. To identify autoantibody targets, the authors used immunoprecipitation coupled to mass spectrometry and confirmed these findings with cell-based assays and ELISA. Tissue-based and cell-based assays were imaged using wide-field and confocal microscopy.

Diagnostics of autoantibodies included screening for antinuclear antibodies (ANA), antibodies against extractable nuclear antigens, anti-neutrophil cytoplasmic antibodies (cANCA and pANCA), and antibodies against several other related antigens.

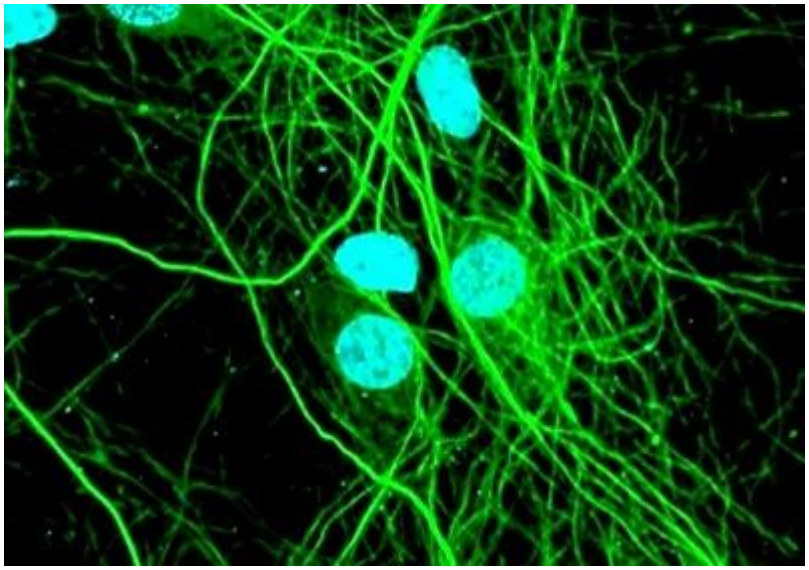
Results

The study included 50 patients with peripheral neurological symptoms after COVID-19 vaccination and 35 age- and sex-matched vaccinated healthy controls. The mean age of patients with PCVS was 41 years (ranging from 21 to 62 years), and 60% were females. All but one (98%) of the PCVS patients were vaccinated with the mRNA vaccine, with symptom onset from one hour to 30 days following the vaccination (median= 3 days).

The most common symptom of peripheral nervous system disorders was paresthesia, reported by 56% (n=28) of PCVS patients. 22% of PCVS patients (n=11) reported neuropathic pain, 22% (n=11) reported fasciculations, and 22% (n=11) reported myalgia.

Other neurological symptoms were also reported. 46% (n=23) of PCVS patients reported fatigue, 36% (n=18) cognitive deficits, and 30% (n=15) headaches.

Routine laboratory tests, electrophysiological examination, and skin biopsy did not reveal relevant pathological findings.



Autoantibody identification

ANA test was positive in 24% (11/45 patients) diagnosed with PCVS (titer ranging from

1:160 to 1:640), and cANCAs were elevated in one patient with PCVS. These findings are consistent with recent results showing *de novo* production of antinuclear antibodies in 29% of healthcare workers after three mRNA COVID vaccinations.
https://discovermednews.com/healthcare-workers-de-novo-autoantibody-production-after-three-doses-of-anti-sarscov-2-vaccines/

Autoantibodies against peripheral nerve structures were more frequent in PCVS patients than in healthy controls. In 18% (9/50) of patients diagnosed with PCVS, the testing of sera for autoreactivity against murine sciatic nerve identified IgG binding to various nerve structures. Broad paranodal binding was identified in only one healthy control subject. Specific binding was not detected in 41 out of 50 PCVS patients and in 34 out of 35 healthy controls.

IgG binding was directed against axons (n=4), paranodes (n=5), Schmidt-Lanterman incisures (n=2) and Schwann cell nuclei (n=1). There was no relevant IgM or IgG binding to gangliosides, showing that gangliosides were not targets for autoreactive IgGs.

To identify the unknown targets of the autoreactive IgGs, the authors performed immunoprecipitation coupled to mass spectrometry with the strongest binding sera against paranodes and Schmidt-Lanterman incisures (patient no.40) or against axons and Schwann cell nuclei (patient no.12). The results revealed that neurofilament subunits NF-L and PRPH were potential autoantibody targets in the serum of patient no.12.

Cell-based assays confirmed these findings and identified NF subunits NF-H, NF-M, and PRPH as autoantibody epitopes in the serum of patient no.12. In the serum of patient no.4o, which was also positive for cANCAs, Psip1 (DFS-70) was identified as a target for autoreactive IgGs. ELISA also confirmed autoreactivity against DFS-70.

Conclusion

This study has shown that the serum prevalence of autoreactive IgGs against peripheral nerve structures was significantly higher in PCVS patients than in healthy controls. IgG binding was directed against axons, paranodes, Schmidt-Lanterman incisures, and Schwann cell nuclei. None of the PCVS sera bound to gangliosides. Subsequent target identification in two PCVS patients revealed various NF subunits and DFS-70 as autoantibody epitopes.

The authors discussed the origin of these autoreactive IgGs. They suggested that the vaccination itself triggered these autoantibodies or they were already present before

vaccination, as autoantibodies are generally present in healthy individuals. Vaccination can trigger different mechanisms of antibody formation, such as molecular mimicry, the formation of immune complexes with vaccine components, non-specific B-cell activation, and subsequent expansion in a pro-inflammatory milieu.

The authors suggested that further studies should elucidate the presence of autoantibodies against neurofilaments and cell nuclei in the PCVS spectrum and determine their biomarker potential.

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Journal Reference

Arlt F, Breuer A,Trampenau E et al. High serum prevalence of autoreactive IgG antibodies against peripheral nerve structures in patients with neurological post-COVID-19 vaccination syndrome. Front. Immunol 2024; 15: 1404800. (Open Access) https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2024.1404800/full