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Post-vaccination syndrome

OPINIONS

ELLING ULVESTAD

elling.ulvestad@helse-bergen.no
Elling Ulvestad MD, PhD, head of the Department of Microbiology, Haukeland University Hospital, and professor at the Department of Clinical Science, University of Bergen
The author has completed the ICMJE form and declares the following conflicts of interest: he has acted as an expert witness in court cases related to vaccine-related injuries and has written a report on COVID-19 vaccines and their potential adverse effects for the Norwegian Nurses Organisation.

Onset of a prolonged pain and fatigue syndrome following vaccination against SARS-CoV-2 is likely linked to dysfunctional regulation of the immune system.

During the mass COVID-19 vaccination campaign, health authorities in several countries received reports of patients developing persistent symptoms such as fatigue, headache, myalgia and cognitive difficulties. Norwegian data provide an estimate of incidence. Between December 2020 and March 2025, more than 13,896,000 doses of COVID-19 vaccines were administered, with 448 reports of adverse effects related to persistent headache (> 6 months) and 67 reports of long-term fatigue (> 3 months) (1). These symptoms, which are now referred to as post-vaccination syndrome or post COVID-19 vaccination syndrome (PCVS), share several characteristics with chronic fatigue syndrome; however, while chronic fatigue syndrome is rarely linked to a specific cause, post-vaccination syndrome is, by definition, preceded by vaccination.

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Whether post-vaccination syndrome is caused by vaccines other than those for SARS-CoV-2 remains unclear, largely due to a lack of robust case series and rigorous epidemiological studies. The absence of methodological rigour is particularly problematic, as an inappropriate study design could obscure the presence of post-

vaccination syndrome. For example, when some patients reported post-vaccination fatigue following vaccination with Pandemrix against swine influenza in 2009, an epidemiological study was conducted to assess whether Pandemrix increased the risk of chronic fatigue syndrome (2). By linking data from patient registries and vaccination records, researchers were able to show that there was no increased risk of chronic fatigue syndrome following vaccination. However, the study was not able to determine whether Pandemrix increased the risk of post-vaccination syndrome, as neither the medical history nor current health status of patients was verified. A thorough clinical assessment of the vaccinated patients might have allowed for a more nuanced conclusion.

Immunopathogenesis

It is assumed that the relationship between vaccination and disease is mediated via dysregulated activation of the immune system (3, 4), and several studies attempting to test this hypothesis have been published (4–7). Due to difficulties in recruiting patients, study populations are small. In addition, variable and suboptimal control group selection makes it difficult to draw firm conclusions as to whether the immunological characteristics identified in patients with post-vaccination syndrome are specific to the condition or also found in patients with similar or other conditions.

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A study of patients with long COVID sought to address this limitation (7). In this study, altered levels of inflammatory molecules and autoantibodies were also observed in patients with post-vaccination syndrome, and the authors suggested that these findings may be consistent with a hypothesis in which the symptoms in the two disease groups are characterised by different immunopathogenic mechanisms. Thus, although the results across studies support the research hypothesis, further studies involving large and heterogenous patient and control groups are needed to establish a causal relationship.

Future research

Research aimed at mapping the clinical manifestations and pathogenesis of post-vaccination syndrome is still at an early stage. However, clinical and immunological evidence has already been obtained from a relatively large cohort of patients, indicating that there are reasonable grounds to assume that SARS-CoV-2 vaccines may lead to a condition consistent with post-vaccination syndrome.

US health authorities have acted on this knowledge, and the Food and Drug Administration has therefore instructed the vaccine manufacturer Pfizer to conduct a prospective, placebo-controlled, randomised study to evaluate symptoms and

biomarkers of post-vaccination syndrome in recipients of a next-generation mRNA vaccine (8). In doing so, the health authorities seek to ensure that manufacturers take responsibility for funding studies that can help clarify key issues in vaccinology.

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