Commentary. Discussion. Opinion.

THE PERFECT STORM RELATIONSHIP BETWEN VACCINATION-INDUCEED DISORDERS AND ILLNESS MANIFESTED BY POST-COVID-19 LONG HAULERS

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Severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2), the cause of coronavirus disease 2019 (Covid-19), has not only created an acute worldwide pandemic but also chronic adverse health effects in a substantial percentage of survivors.

The latter disorder's clinical features include disabling fatigue, cognitive dysfunction, anosmia, weakness, dyskinesias, shortness of breath, paresthesias, and widespread generalized pain. Individuals manifesting chronic post-Covid-19 phenomena have been referred to as long haulers [1], and outpatient clinics have been established at many medical centers to study and treat them. Their symptoms can occur even in the absence of events transpiring during the acute phase of Covid-19 infection, such as cytokine storm, viral brain invasion, strokes from clotting system activation, heart failure, and seizures.

Several Covid-19 neutralizing antibodies have been shown to cross-react with self-antigens present in the central nervous system (CNS) [2]. Neuronal membrane components, microglia cells, and vascular endothelial cells are typical targets. In addition, non-viral autoantibodies (e.g., +ANA, + Rheumatoid Factor) and autoreactive T cells frequently appear after Covid-19 viral clearance and cessation of the acute viral illness [3,4]. Post-infectious autoantibody production is not unique to Covid-19, as similar phenomena have been observed following disseminated herpes simplex and tuberculosis infections [4].

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Various immunization-induced disorders are known to be autoimmune processes mediated by cross-reacting autoantibodies that share specific antigenic specificity with vaccine components [5]. Examples include Guillain-Barre syndrome, systemic lupus erythematosus, and rheumatoid arthritis following influenza vaccination. Although such occurrences are infrequent, they are well recognized as legitimate events. A separate category of vaccination-induced disorders encompasses overlapping features of the various neurologic fatiguing syndromes. These are far more complex and arise from the plausible interactions of (a) multiple indigenous factors (e.g., innocuous channelopathies; reduced hepatic P450 enzyme activity towards xenobiotics; regulatory T cell dysfunction); (b) multiple hidden chemicals in vaccine ingredients; (c) abnormalities in mitochondrial quantum tunneling; (d) reactivation of previously acquired viruses; (e) microbiome disturbances; (f) epigenetic alterations; and (g) the cumulative effects of increasing numbers (and earlier and earlier administration) of multiple childhood vaccines, whereby the most recent immunization may be "the straw that broke the camel's back" [6-8]. As one can appreciate from this complexity, autoimmune mechanisms are not the initiators of this type of vaccination-induced disorder. However, once such a disorder is underway, all of these integrated variables can participate in the delayed production of multiple autoantibodies, which, in turn, can create secondary amplification loops that circuitously augment and perpetuate the initial acute adverse event [6-8]. Stated another way, disease causation mechanisms that initiated one or more acute vaccination-related neurological events can subsequently be replaced weeks later by latent autoimmune mechanisms that evolved more slowly before becoming clinically relevant. These secondary amplification loops may then indefinitely prolong the initial events and make them chronic. Such a process amounts to "a perfect storm." It is directly

analogous to the transformation occurring in some Covid-19 recipients who find their initial infectious illness replaced by a bizarre and chronic disabling process encompassing autoimmune features. Months later, either of these scenarios could erroneously be interpreted by other physicians as two separate events, whereby the acute vaccination reaction or the acute infection-related hospital course are nullified as causative factors in the perpetual chronic sequelae.

Does the presence of cross-reacting neutralizing antibodies and/or the development of autoantibodies in Covid-19 patients define the population at risk for becoming long haulers? That remains delineated, but, likely, researchers have only scratched the surface for the numbers and types of antibodies that can occur. In vaccination-induced disorders resembling neurologic fatiguing syndromes, multiple autoantibodies have been implicated in causing disease prolongation and eventual chronicity [8]. These autoantibodies may be directed at various components of sensory nerves, motor nerves, autonomic nerve receptors, dorsal root ganglia, and even the brain.

Typical targets include proteins regulating sodium, potassium, and calcium channel functions; glycoproteins, proteoglycans, and individual matrix macromolecule components (e.g., heparin sulfate, chondroitin sulfate); enzymes (e.g., GAD65, which catalyzes the conversion of glutamate to gamma-aminobutyric acid); phospholipids; neurotransmitters; microglia cells; and neuromuscular junctions. Antibodies to heparin sulfate are particularly interesting for two reasons: (1) heparin sulfate can function as a receptor for both protease enzyme activity and for inhibitors of protease enzymes; and (2) heparin sulfate, like chondroitin sulfate, is often physiologically incorporated into the protein apparatus comprising sensory and CNS receptors. These glycosaminoglycans are also crucially involved in the normal development of one's entire nervous system.

The population at risk for vaccination-induced disorders encompassing overlapping features of the various neurologic fatiguing syndromes does not appear to be individuals with established systemic connective tissue diseases. Nor does the risk appear to lie in individuals with a family history of systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, etc. Contrast this with recent USA prevalence data revealing positive antinuclear antibodies in 12 percent of asymptomatic general population inhabitants (20 percent in asymptomatic teenagers aged 13 to 19) [9].

Are these +ANA cohorts more susceptible to developing secondary autoimmune amplification loops that confer chronicity to acute vaccine-related events (even though the hidden chemicals in vaccines that initiate such events can readily trigger a secondary wave all by themselves)? Similarly, does the presence of a silent +ANA in patients subsequently infected with Covid-19 make them more susceptible to become long haulers? And is this increase in +ANA's (which used to be 3 percent of asymptomatic individuals 45 years ago) a result of childhood vaccination policies run amok?

Covid-19 has greatly expanded our knowledge and insights into autoimmunity and inflammation, and knowledge of hidden chemical vaccine ingredients has greatly expanded our knowledge of vaccine toxicity. The two newly released Covid-19 vaccines manufactured by Pfizer and Moderna employ brilliant technology by delivering mRNA in vivo to human cells to initiate the process of viral spike protein synthesis, thereby prompting reactive anti-viral antibody production. The nanoparticles utilized in this delivery process have varied compositions and varied biological properties that are, in theory, supposed to be biocompatible, biodegradable, non-toxic, non-immunogenic, and water-soluble [10]. They must also demonstrate resistance to degradation, explicit cellular trafficking via endocytosis and pinocytosis, and some adjuvant activity. Accomplishing all of this introduces a long list of ingredients into nanoparticle synthesis [11], namely: (a) various lipids (ALC-3015, ALC-0159, DPSC, cholesterol); (b) organic solvents and polymers, some of which are neurotoxic and renal toxic (poloxamer 188, phospholipon 90H, cyclohexane), and these may be present under other labels such as polyoxypropylene, polyoxyethylene, pluronic F-68 and F-127; (c) silicones and silica interspersed between lipid layers; (d) Tego care 450 (a surfactant and emulsifier); (d) compritol (a lipid surfactant and emulsifier); (e) polyethylene glycol (PEG 2000, PEG 4500, PEG 400, capable of causing allergic reactions); (f) Tween 85 (the surfactant and emulsifier polysorbate 85); (g) Tween 80 (the surfactant and emulsifier PS-80, a sorbitan with residual sorbitol after its synthesis); (h) sodium alginate (cross reacts with seafood allergies); (i) sodium dihydrogen phosphate dihydrate (a pH buffer and emulsifier, manufactured from sodium carbonate which itself contains residues of silica); and (j) trisaminomethane (a pH buffer). Once hundreds of millions of individuals receive these expansive vaccine cocktails, the routine process of passive and active surveillance programs will hopefully and accurately assess

the frequency and severity of any adverse reactions (both acute and chronic). However, a recent publication has cast doubt on the reliability and accuracy of vaccine surveillance data [12]. This adds another dimension to the long-running controversy regarding vaccine safety.

Special attention must also be directed to the safety and efficacy of Covid-19 vaccines in patients with an organ transplant. This must be balanced against the expectation of reduced vaccine efficacy incurred when one is ingesting immunosuppressive drugs to prevent rejection. Kidney transplant recipients are routinely given vaccinations to prevent hepatitis B, influenza, pneumococcal infections, and the varicella-zoster virus's reactivation. The rationale for this is straightforward: the risk of vaccine-induced immunologically mediated transplant rejection in first-year recipients is lower following these four immunizations than the risk of transplant rejection following any one of these spontaneous infections. However, comparable long-term data for repetitive vaccinations in five and ten-year recipients are lacking. If "booster" Covid-19 vaccines wind up being repetitively administered every year, the risk-benefit analysis in renal transplant survival may be significantly altered. Besides, it remains to be seen if the Pfizer and Moderna vaccines favorably alter the excessive disease severity and higher mortality rates that renal transplant patients experience after acquiring Covid-19 infections.

Hopefully, vaccines for Covid-19 will result in far fewer long haulers cases by reducing the severity of Covid-19 exposures. Acute and chronic vaccination-induced disorders attributable to Covid-19 immunizations need to be carefully assessed over intervals of several weeks because of the potential latency in mechanisms of disease causation that transcend anaphylaxis and allergic reactions. These mechanisms may encompass phenomena that few clinicians are likely to be aware of, namely: (a) the antigenic portions of a vaccine itself, via cytokine induction, can transiently suppress the liver's cytochrome P450 enzyme activities against a variety of drugs [13]; and (b) chemicals called ethylenes are known inhibitors of cytochrome P450 enzyme activity [14]. PEG (polyethylene glycol) is present in both Pfizer and Moderna Covid-19 vaccines, and PEO (polyethylene oxide) is also present in the Moderna vaccine. In vivo reductions in the pharmacologic metabolism of drugs may have relevance for many of the 1400 deaths reported to date following Pfizer and Moderna vaccinations, most of which have occurred in elderly patients who, in turn, are plausibly ingesting numerous medications. The implications for profound, unanticipated medication-induced hypoglycemia in diabetics, and potential iatrogenic cardiovascular events from unanticipated serum elevation of arrythmia medications, are self-explanatory. Stated another way, elderly patients taking a variety of drugs can potentially succumb to inadvertent drug overdosage following either of the above two vaccines.

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