LETTER TO THE EDITOR

Sir,

I am a pediatric specialist caring for children with the multisystem inflammatory syndrome (MIS-C). I am concerned about the possibility that the new vaccines aimed at creating immunity against the SARS-CoV-2 spike protein (including the mRNA vaccines of Moderna and Pfizer–BioNTech) have the potential to cause microvascular injury to the brain, heart, liver and kidneys in a way that is not currently being assessed in safety trials of these drugs.

Puntmann et al. [1] showed that the prospective study of 100 German patients recently recovered from Covid-19 revealed significant cardiac involvement on cardiac MRI scans in 78% of them, on average 2.5 months after their recovery from the acute illness. Two-thirds of these patients were never hospitalized, and there was ongoing myocardial inflammation in 60%. The abnormalities occurred independent of preëxisting conditions, severity of the initial disease, and overall course of the acute illness. These kinds of changes may not have immediate functional consequences, as suggested by the study of Sechi et al. [2]. They examined EKG and echocardiograms for 105 consecutive Italian patients hospitalized with Covid-19 and found no clear differences compared with matched controls, or between patients with different levels of disease severity, with regard to structural or functional abnormalities. It is possible that non-hospitalized patients face more long-term cardiac consequences of infection, and short-term recovery does not guarantee an absence of risk for long-term cardiac complications.

Magro et al. showed that there is complement-mediated damage even in grossly normal skin of coronavirus-infected individuals [3]. They also showed [4] that ACE2 receptor expression is highest in the microvasculature of the brain and subcutaneous fat, and to a lesser degree in the liver, kidney and heart. They demonstrated that the coronavirus replicates almost exclusively in the septal capillary endothelial cells of the lungs and the nasopharynx, and that viral lysis and immune destruction of those cells releases viral capsid proteins (or pseudovirions) that travel through the circulation and bind to ACE2 receptors in these other parts of the body—leading to mannan-binding lectin complement pathway activation that not only damages the microvascular endothelium but also induces the production of many pro-inflammatory cytokines. Meinhardt et al. [5] show that the spike protein in brain endothelial cells is associated with formation of microthrombi, and like Magro et al. do not find viral RNA in brain endothelium. In other words, viral proteins appear to cause tissue damage without actively replicating virus.

Is it possible the spike protein itself causes the tissue damage associated with Covid-19? Nuovo et al. [6] have shown that in 13/13 brains from patients with fatal COVID-19, pseudovirions (spike, envelope and membrane proteins) without viral RNA are present in the endothelia of cerebral microvessels. Furthermore, tail vein injection of the full length S1 spike subunit in mice led to neurological signs (increased thirst, stressed behaviour) not evident in those injected with the S2 subunit. The S1 subunit localizes to the endothelia of microvessels in the mouse brain, and is a potent neurotoxin. So the spike S1 subunit of SARS-CoV-2 alone is capable of being endocytosed by ACE2-positive endothelia in both human and mouse brain, with a concomitant paucicellular microencephalitis that may be the basis for the neurological complications of COVID-19. The Pfizer–BioNTech vaccine (BNT162b2) is composed of an mRNA that produces a membrane-anchored full-length spike protein. The mouse studies suggest that an untruncated form of the S1 protein like this may cause a microvasculopathy in tissues that express much ACE2 receptor. A truncated form of S1 was much less damaging in mice.

While there are pieces to this puzzle that have yet to be worked out, it appears that the viral spike protein that is the target of most SARS-CoV-2 vaccines so far (including the Oxford–AstraZeneca and Janssen–Johnson & Johnson vaccines) is also one of the key agents causing the damage to distant organs, which may include the brain, heart, lung and kidney. Before any of these vaccines are approved for widespread use in children, it is important to assess in vaccinated subjects the effects of vaccination on the heart (perhaps using cardiac MRI, as did Puntmann et al.). Vaccinated patients could also be tested for distant tissue damage in deltoid area skin biopsies, as employed by Magro et al. [3]. Important as it is to quickly arrest the spread of the

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virus by immunizing the population, it would be worse if hundreds of millions of children were to suffer long-lasting damage to their brain or heart microvasculature as a result of failing to appreciate in the short term an unintended effect of full-length spike protein-based vaccines on these other organs.

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