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Post-COVID-19 Syndrome vs. Consequences of Vaccination with Special Reference to Cardiovascular Conditions

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Abstract

Consequences of COVID-19 vaccination partly overlap with symptoms of post-COVID-19 syndrome. Putative mechanisms are also overlapping: endothelial damage and hyper coagulation, hypoxia, autoimmunity, inflammation, downregulation of angiotensin-converting enzyme. It can be reasonably assumed that effects of viral spike protein, observed in COVID-19, would to some extent appear also after administration of vaccines containing spike protein or inducing its synthesis. Vaccination with new vaccines entails known and unknown risks. Children, young adults and other people can mount their own immunity to SARS-CoV2. Admittedly, postvaccinal cardiovascular events are usually benign and self-limited. However, pressures for rapid approval of vaccines can result in the distribution of preparations with unstable quality, which depends on the manufacturing standards. There have been few reports from Russia about blood clotting-related, cardiovascular and other adverse effects after vaccinations. The number of undetected cases is unknown. Reports on side effects of some renowned vaccines do not imply higher risks but indicate that they are better studied than those coming from less open societies tolerating scientific misconduct. In conclusion, healthcare providers should be vigilant for cardiovascular and other side events after COVID-19 vaccinations; further research especially of long-term risks is needed.

Keywords: COVID-19; Vaccination; Cardiovascular; Post-COVID-19 condition.

Abbreviations: PCS: Post-COVID Syndrome; SP: Spike protein; ACE2: Angiotensin-converting enzyme 2 receptors; IL: Interleukin; TNF-α-Tumor necrosis factor α; CI -Confidence interval; PF4 - Platelet factor 4.

Introduction

It has been argued that COVID-19 as a cause of death was overestimated and co-morbidities undervalued [1]. "Died with COVID-19" is not the same as "died of COVID-19". In terms of years of life lost, the current pandemic will presumably score similarly to the 1957 and 1968 influenza pandemics in view of the advanced mean age of COVID-19 fatalities [2]. Excessive anti-epidemic measures and lockdowns are harmful for the economy as well as for the public health. The irrational use of health resources interferes with the regular patient care. In retrospect, the increase in mortality from different causes will probably be ascribed to COVID-19, and subsequent mortality decrease attributed to successful anti-epidemic measures including vaccinations. The topic is inflated and mixed with politics. The effectiveness of travel restrictions, quarantines, and contact tracing is questionable because SARS-CoV-2 is already spreading worldwide like influenza did in the past. Historical data suggest no change in the speed of flu spread despite the proliferation of travel and human contacts. Travel restrictions can curb the international spread only if immediate and total [3]. Numerous mild and asymptomatic cases are inevitably missed.

Post-COVID syndrome (PCS)

Patients with prior COVID-19 infection may develop chronic sequelae, including respiratory, cardio- and cerebrovascular disease, diabetes mellitus, cognitive and psychiatric derangements [4-7]. This mini-review is focused on cardiovascular conditions. The following has been reported after COVID-19: myo- and pericarditis, myocardial ischemia, atrial fibrillation, exertional dyspnea, dysrhythmias, heart failure, thromboembolic disease, orthostatic hypotension, fatigue, dizziness and increased resting heart rate [4,8]. Chest pain and palpitation are common symptoms of PCS [4,5,9]. Some recovering patients remain with a decreased cardiac reserve and deregulation of the renin-angiotensin system [5].

Putative mechanisms of the cardiovascular damage include direct viral injury, downregulation of ACE2, inflammation of microvessels, of peri- and myocardium including the conduction system [5]. SARS-CoV-2 uses its Spike Protein (SP) to bind to Angiotensin-converting enzyme 2 receptors (ACE2), which are located on the surface of endothelial and some other cells [7]. Damage to the blood vessel endothelium in acute COVID-19 infection may lead to thrombophilia resulting in micro- and macro-thrombus formation. Vascular lesions and hypoxia prolong the procoagulatory state beyond the acute phase of the disease. This occurs synergistically with autoimmunity, which further contributes to the process by increased production of pro-inflammatory cytokines: interleukin 6 (IL-6), IL-1, IL-10, Tumor Necrosis Factor α (TNF-α) and others [7].

Consequences of vaccination

Cardiovascular manifestations of PCS and corresponding mechanisms partly overlap with those after COVID-19 vaccinations [4-10]. Among others, an area of overlap is related to SP. It can be reasonably assumed that the impact of SP observed in COVID-19 would occur to some degree also after administration of vaccines containing SP. The SARS-CoV-2 virus uses ACE2 as a receptor, which may lead to the ACE2 degradation and angiotensin-II-mediated tissue injury [11]. The downregulation of ACE2 by SP can lead to endothelial damage and cardiovascular derangements [12,13]. Besides, SP binds to ACE2 receptors on platelets and is presented to the immune system potentially triggering autoimmunity [11]. The endothelial damage together with platelet activation provokes coagulopathy and thrombophilia up to the development of vaccine-induced thrombotic thrombocytopenia [14].

Significantly more cases of myo- and pericarditis than expected have been recorded after COVID-19 vaccinations. The supposed mechanism is immune response with inflammatory reactions to SP or SP-coding nucleic acids [15,16]. In a population-based cohort study (vaccinated with mRNA-based vaccine vs. control; approximately 885,000 subjects in each cohort), the vaccination was associated with enhanced risk of myocarditis: the risk ratio was 3.24, 95% Confidence Interval (CI) 1.55 to 12.44 [17]. In a group of persons aged 12-39 years, who had recently received a second dose of mRNA-based COVID-19 vaccine, the rate ratio for myocarditis was 10.8 compared to the general population (95% CI 3.2 to 49.0) [18]. The symptoms of myocarditis usually start 2-4 days post-vaccination being more frequent after the second dose of mRNA vaccines. Chest pain was present in all patients; 67% of them had fever. Arrhythmias or heart failure were encountered in more severe cases [19]. Furthermore, myalgia was observed in 21% of athletes after the first dose of mRNA-based vaccine, rising to 37%, following the second dose [20]. Finally, SP has been shown in vitro to penetrate into cell nuclei and inhibit DNA repair [21].

Moreover, SP binds to T cell receptors and enhances immune reactions [22,23]. Endothelial cells bearing SP or other viral antigens are potential targets of the host immune system. This may result in vasculitis, which is of particular importance for the brain, where it may lead to disruption of the blood-brain barrier and perivascular encephalitis. Neurological side effects of SARS-CoV-2 vaccinations are usually mild; however, some cases have been severe, required hospitalization and admission to intensive care units [24]. Encephalitis developed significantly ($p<0.001$) more often after the use of adenoviral vector than after mRNA vaccines: 79 cases in 99.3 million doses vs. 20 cases in 110.6 million [25]. Cases of facial palsy, Guillain-Barre syndrome and transverse myelitis have been documented [15,24,26]. Statistics are of questionable reliability; adverse effects may be missed, ascribed to other causes or obfuscated to comply with actual or presumed directives - a known phenomenon e.g. in the former Soviet Union [27-31]. In want of reliable data, the role of theoretic argumentation increases.

Apart from SP, blood clotting derangements may be caused by adenoviral vectors in vaccines [16]. There is evidence of synergism between the vectors and SP [32]. Adenoviral vectors elicit cellular and humoral immune responses, bind to circulating platelets inducing their activation and aggregation. Adenoviral vector vaccines may trigger autoimmunity with autoantibodies to the Platelet Factor 4 (PF4). The chain of events includes microvascular damage, platelet activation with PF4 release, formation of DNA-PF4, PF4-directed autoimmunity and vaccine-associated immune thrombosis [12]. The above mechanisms provide an explanation for the association of adenoviral vector-based COVID-19 vaccines with cerebral events such as venous sinus thrombosis, ischemic and hemorrhagic stroke as well as splanchnic vein thrombosis, pulmonary embolism and disseminated intravascular coagulation [15,24,32,33]. Among cases with thromboembolic events have been relatively many young women known to be more susceptible to certain autoimmune conditions [12,34,35].

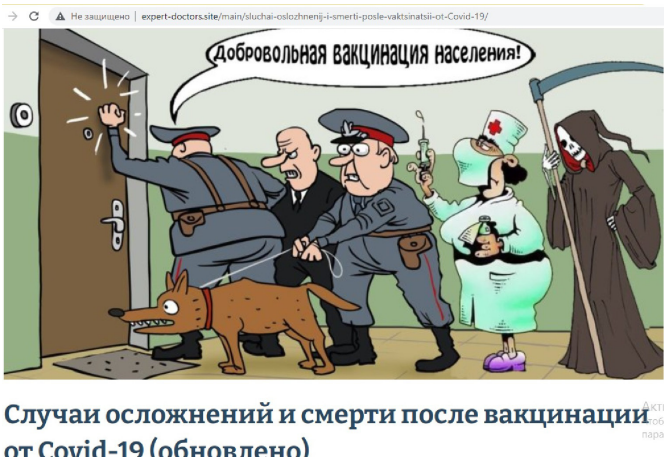

Figure 1: Compulsory COVID-10 vaccination. Adapted from [28].

Discussion

Consequences of vaccination partly overlap with symptoms of PCS. Putative pathogenetic mechanisms are also overlapping: endothelial damage and hypercoagulation, hypoxia, autoimmunity, inflammation and downregulation of ACE2 enhancing activity of Angiotensin II. It can be reasonably assumed that effects of SP, observed in COVID-19, would to some extent appear also after administration of vaccines containing SP or inducing its synthesis. SP originating from the virus or from vaccines, binding with ACE2, may cause an imbalance of ACEs, which plays a role both in COVID-19 and vaccine-related complications. Reportedly, the heart rhythm is affected by ACEs; and their deregulation can provoke arrhythmias [36]. According to another review, thrombotic events were the most common complications of COVID-19 vaccinations [37]. Besides, adverse effects may be caused by adenoviral vectors contributing to blood clotting derangements and triggering immune responses. Admittedly, postvaccinal cardiovascular events are usually benign and self-limited [38]. However, pressures for rapid approval of vaccines can result in the distribution of preparations of unstable quality, which depends on the manufacturing standards.

Compulsory vaccination with new vaccines entails known and unknown risks. Although SARS-CoV-2 vaccinations are usually depicted as safe, concerns are backed by increasing numbers of reports on moderate-to-severe side effects [24]. Children, young adults and many other people can mount their own immunity to SARS-CoV2 undergoing acceptably low risk. There is an opinion that it is unethical to impede the access to natural immune response [39]. A recent systematic review demonstrated that natural immunity in patients recovering from COVID-19 is at least equivalent to the protection by vaccination of COVID-naïve people, with the possibility of enhanced durability of protection from natural immunity [40].

In future, countries implementing strictest measures might find themselves with a weaker protection by natural immunity. The vaccine quality e.g. undeclared components are of importance for the risk of side effects. In addition to adenoviral vectors, vaccines may contain various substances of human and viral origin, proteins and other contaminants [12,32]. Officially tested preparations are not necessarily always the same as those administered to the broad public. Political pressures for rapid approval of vaccines can result in distribution of preparations of questionable quality [41]. A winner of "the race for a vaccine against SARS-CoV-2" [42] may end up in a mass vaccinations with suboptimal vaccines. There have been reports from Russia about blood clotting-related, cardiovascular and other adverse events after vaccinations [27,28,43-46]. A case is known to us where a 65-years-old patient was vaccinated with Gam-COVID-Vac one year after a nearly asymptomatic COVID-19 infection, and after that has developed symptoms compatible of PCS: Asthenia, shortness of breath, cardiac arrhythmia, numbness of limbs and herpes zoster. Cognitive impairments have been noticed as well. Intense headache was the leading symptom immediately after the vaccination [10]. The number of unreported cases is unknown. The documentation reliability of side effects remains questionable, as it has been the case with some other medical statistics [27,28,30,44]. Of note, reports on side effects of some renowned vaccines do not imply higher risks but indicate that they are better studied than those coming from less open societies tolerating scientific misconduct [31]. Theoretically, all the above considerations may pertain to some extent to different vaccine types: inactivated, recombinant protein, DNA and others. A probable way to eliminate some side effects is the developing synthetic monoantigenic vaccines [42].

Conclusion

Effects of SP, observed in COVID-19 patients, can to some extent appear also after administration of vaccines containing SP. PCS cannot always be clearly differentiated from post-vaccination events. In addition, adverse events after vaccinations may be caused by adenoviral vectors, other components and contaminants in vaccines, which may depend on the manufacturing quality. Blood clotting disorders are of particular importance [47]. The above can be regarded as arguments against indiscriminate vaccination especially after COVID-19 infection. The author agrees that the "vaccination of COVID-recovered individuals should be subject to clinical equipoise and individual preference" [40]. A promising research direction would be experiments in animal models using various vaccines, comparing with controls the levels of blood clotting (e.g. D-dimer) and other relevant markers [48]. It would be interesting to carry out a large-scale survey among individuals who first experienced COVID-19 infection and later the vaccination asking a question, when the symptoms were more severe. However, results of such survey may be biased because some people would respond in the questionnaire what they perceive as officially or unofficially prescribed. Apparently, some scientific writers conform to the same principle: the rarity of reports on the side effects of COVID-19 vaccinations may be caused by local policies discouraging such reporting [49]. In conclusion, healthcare providers should be vigilant for cardiovascular and other side events after COVID-19 vaccinations; further research especially of long-term risks is needed.

Based on the experience with influenza, it has been predicted that "the future… will be full of continuous alarms and possible declarations of pandemics" [50,51]. Furthermore, "we have little reliable evidence on the effects of influenza vaccines. What we do have is evidence of widespread manipulation of conclusions and spurious notoriety of the studies" [51]. The situation around COVID-19 seems to be analogous. At least in Russia, the mass use of domestic vaccines of questionable quality should be discontinued.

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