



## Letter to the Editor

## Encephalitis, myocarditis, and thrombocytopenia after COVID-19 mRNA vaccination: Clinical and pathophysiological considerations

## ARTICLE INFO

## Keywords

COVID-19  
Hypersensitivity  
Myocarditis  
Myocarditis  
Thrombocytopenia  
Vaccination

COVID-19 vaccination has been associated with rare neurological, cardiac and hematological complications but their causal relationship is not yet fully established. We have read with interest the paper published in *Journal of Neuroimmunology* (Asaduzzaman et al., 2022) concerning, a 15-year-old girl who developed the following symptomatology after the second dose of Pfizer BioNTech (BNT162b2) COVID-19 vaccine: Fever and diarrhea 1 day after receiving the vaccine, marked thrombocytopenia during the initial blood count examination, symptoms and signs suggesting encephalopathy such as carpopedal spasm in both hands, altered consciousness leading to unconsciousness and attacks of convulsions well responding to methylprednisolone injections. Six days later the patient developed palpitations, electrocardiographic diffuse T wave inversion, hypokinetic anterior wall with reduced ejection fraction (46%) in echocardiography. The troponin, creatine kinase and its MB isoenzyme were elevated supporting the clinical diagnosis of myocarditis.

This case raises important issues, on vaccine-associated encephalitis and blood brain barrier, the classification of myocarditis, the immune-mediated thrombocytopenia and the potential preventive and therapeutic perspectives.

### 1. Encephalitis and COVID-19 vaccines

The brain is protected by the blood-brain barrier which separates the brain from the rest of the body and does not allow foreign substances from entering the brain. The arising questions, therefore, include: can vaccines cross the blood-brain barrier and go into the brain? is any vaccine excipient able to induce immune encephalitis or hypersensitivity reaction in the brain? Whereas the brain, does not suffer from hypersensitivity reactions because IgE antibody complexes do not cross the blood-brain barrier, it contains a number of mast cells which when degranulate can cause hypersensitivity reactions. The described patient responded significantly to methylprednisolone suggesting underlying immune or hypersensitivity pathogenesis. Indeed, allergic encephalitis caused by wasp sting treated with methylprednisolone and intravenous immunoglobulin has already been described (Maramattom, 2021). We believe that the followings may provide an answer to these questions.

The described patient developed signs and symptoms of encephalitis

after the second dose of Pfizer BioNTech (BNT162b2) COVID-19 vaccine. Vaccines contain excipients that are necessary to support and optimize the properties of the active vaccine ingredients. The Pfizer BioNTech vaccine contains polyethylene glycol excipient, also called macrogol (E1521). Polyethylene glycol-coupled polymers can cross both the blood-brain barriers and the blood-spinal cord and they have been widely used as drug carriers (Kong et al., 2017). Polyethylene glycols can act as allergens and immediate hypersensitivity reactions have already been reported (Nilsson et al., 2021). Moreover, the encephalitis symptoms appeared after the second dose of the vaccine and the existence of pre-formed antibodies, including those directed against polyethylene glycol can not be excluded.

### 2. Myocarditis and COVID-19 vaccines

Myocarditis is a myocardial inflammatory disease in the absence of acute or chronic coronary artery disease as in the described patient. Proper definition and differentiation of myocarditis caused by vaccines, drugs, or substances has not yet been established and there is still confusion on its definition and classification. We, therefore, have classified (Kounis et al., 2021) the myocarditis on causative, histological and clinicopathological criteria as follows:

1. Causative including viral, bacterial, chlamydial, fungal, protozoal, trypanosomal, rickettial, toxic and hypersensitivity myocarditis.
2. Histological including eosinophilic, hypersensitivity, giant cell, granulomatous, histiocytic, lymphocytic, lymphohistiocytic myocarditis.
3. Clinicopathological as fulminant, acute, chronic active, chronic persistent, myopericarditis.

According to a recent report (Oster et al., 2022), based on passive surveillance, the risk of myocarditis after mRNA COVID-19 vaccines, in adolescent and young male individuals was highest after the second dose and was also increased in multiple age and sex strata. The authors suggested that this risk should be considered in the context of the benefits of COVID-19 vaccination.

<https://doi.org/10.1016/j.jneuroim.2022.577988>

Received 19 August 2022; Received in revised form 9 October 2022; Accepted 12 October 2022

Available online 17 October 2022

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### 3. Thrombocytopenia and COVID-19 vaccines

The described patient was found to have marked thrombocytopenia at the time of admission and this was attributed to an autoimmune reaction. Indeed, both mRNA vaccines Pfizer–BioNTech and Moderna have been reported to be associated with secondary immune thrombocytopenia (Lee et al., 2021). Such thrombocytopenia which follows vaccine administration depends on the development of autoantibodies that cross-react with the naturally present antigenic targets on platelets (Cecinati et al., 2013). Platelet surface disposes also high affinity IgE (FcεRI) and low affinity IgE (FcεRII/CD23) receptors, a fact that is not so well known to clinical practitioners (Hasegawa et al., 2001). The existence of this kind of receptors can cause platelet activation by PAF (platelet activating factor) produced by mast cells. The activated platelets aggregate and form thrombosis, and release chemical mediators such as serotonin, thromboxane A2, PF4 (platelet factor 4), PDGF (platelet-derived growth factor), and cytokines such as RANTES (Regulated on Activation, Normal T expressed, and presumably Secreted). The platelet consumption, due to extensive thrombosis, leads to thrombocytopenia (Chong, 1995).

### 4. Perspectives

Creams, ointments, lotions, cosmetics, commonly used by young individuals, dental materials and even laxatives contain also PEG that is able to sensitize its users. Laxatives have been recently associated with Kounis hypersensitivity coronary syndrome (Zuluaga-Gomez et al., 2022). The general population is sensitized to cosmetics or dental materials in 1–5.4% (Lyapina and Stoyanova Dencheva, 2019). Therefore, hypersensitivity encephalitis, myocarditis and thrombocytopenia could be induced by the vaccine excipients. Alternative excipients have been suggested in vaccine manufacturing if vaccine component-induced hypersensitivity is confirmed by systematic future investigations (Warren et al., 2021). Indeed, in a recent report the authors concluded that hypersensitivity to excipients constitutes risk to patients with allergy to PEG and these patients will await new vaccines containing different excipients (Mortz et al., 2022).

It seems that the benefits of vaccination, should be taken into account and the described risks should be also considered in the context of the benefits of COVID-19 vaccination.

#### Funding

No funding was received.

#### Availability of data

All data are available.

#### Code availability

Not applicable.

#### Ethical approval

Not applicable.

#### Patient consent

Not applicable.

#### Author contribution

NGK: concept, writing literature search, discussion, VM, IK, PD, PP: literature search, critical remarks, discussion.

### Declaration of Competing Interest

There are no conflicts of interest.

### Data availability

No data was used for the research described in the article.

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