Caution Regarding Conclusions about COVID-19 Vaccine and Encephalitis

Max Wiznitzer, MD

Rainbow Babies and Children's Hospital, Cleveland, Ohio, USA

Zuhorn et al[1] report apparent autoimmune encephalitis after the AstraZeneca vaccine and discuss its incidence and potential mechanism. However, there are concerns regarding their conclusions.

Onset of the encephalitic symptoms/signs was 5 to 8 days after vaccination. The usual time period between primary vaccination and start of the primary antibody response is 7 to 10 days,[2] with good levels at 14 days and not 7 days for this vaccine (Article Reference 13 Ewer et al).[3] This was the first vaccination for Case 1, with no information about the others. If the mechanism for the presumed autoimmune encephalitis is antibody-mediated, it is unlikely that antibodies, including autoantibodies, were produced in sufficient quantity after the first vaccination to cause any clinical symptoms.

The innate immune response, with its generation of proinflammatory molecules, peaks about 24 hours after vaccination, and drops to baseline within 3 days (Article Reference 7 Herve et al).[4] The authors propose a causal mechanism in which peripheral proinflammatory cytokines cause neuroinflammation by brain microglia activation. The authors' reference (Article Reference 6 Giannotta)[5] is a speculative paper with no supporting literature. Furthermore, peripheral cytokine levels after an mRNA vaccine, if increased, are in the picogram range,[6] whereas levels needed to affect blood–brain barrier integrity and, therefore, enter the brain in sufficient quantity are, at least, in the nanogram range in an in vitro model[7] or associated with cytokine storm. How a transient rise in unspecified peripheral cytokines causes persistent microglia activation and how it leads to an autoimmune encephalitis is not explained or supported by their biologically implausible model.

The encephalitis incidence discussion cites passive reporting systems from several countries. Causal associations and epidemiological conclusions cannot be determined from these data, in part because they are not always validated (https://vaers.hhs.gov/data.html). Therefore, the authors' analyses should be limited and should avoid use of wording such as "responsible vaccinations" that may be interpreted as implying causation.

The authors report an association between COVID-19 vaccination and encephalitis. Unless or until epidemiologic data show a true increase in incidence, it may be prudent to defer ascribing causation and speculation about potential causal mechanisms but, rather, to present the findings and encourage further investigation.

Potential Conflicts of Interest

M.W. serves as an expert witness for the US Department of Health and Human Services in the Vaccine Injury Compensation Program.

Dr Wiznitzer is responsible for the writing and content of the Letter.

References

1. Zuhorn F, Graf T, Klingebiel R, et al. Postvaccinal encephalitis after ChAdOx1 nCov-19. Ann Neurol 2021;90:506–511.
2. Stratton K, Ford A, Rusch E, Clayton EW. *Adverse effects of vaccines: evidence and causality*. Washington, DC: National Academic Press, 2011.
3. Ewer KJ, Barrett JR, Belij-Rammerstorfer S. T cell and antibody responses induced by a single dose of ChAdOx1 nCoV-19 (AZD1222) vaccine in a phase 1/2 clinical trial. Nat Med. 2021;27:270–278.
4. Hervé C, Laupèze B, Del Giudice G, et al. The how's and what's of vaccine reactogenicity. NPJ Vaccines. 2019;4:39.
5. Giannotta G, Giannotta N. Vaccines and neuroinflammation. Int J Pub Health Safe. 2018;3:163.
6. Bergmaschi C, Terpos E, Rosati M, et al. Systemic IL-15, IFN-γ, and IP-10/CXCL10 signature associated with effective immune response to SARS-CoV-2 in BNT162b2 mRNA vaccine. Cell Rep 2021;36:109504.
7. de Vries HE, Blom-Roosemalen MC, van Oosten M, et al. The influence of cytokines on the integrity of the blood-brain barrier in vitro. J Neuroimmunol 1996;64:37–43.

DOI: 10.1002/ana.26289

Reply to "Caution Regarding Conclusions about COVID-19 Vaccine and Encephalitis"

Frédéric Zuhorn, MD,[1] Tilmann Graf, MD,[1] Randolf Klingebiel, MD,[2] Wolf-Rüdiger Schäbitz, MD,[1] and Andreas Rogalewski, MD[1]

We appreciate the comments by Dr Wiznitzer and consider it a cautionary note, consistent with his testimony as an expert witness for the US Department of Health and Human Services in the Vaccine Injury Compensation Program. We agree (and also emphasized in our publication[1]) that causality between the ChAdOx1 nCoV-19 vaccination and encephalitis has not yet been established. In the reported cases, the temporal correlation and the detailed exclusion of other causes drew our attention to the possibility that the encephalitis might be a vaccination side effect.

Dr Wiznitzer expresses skepticism about the postvaccinal clinical time course in our patients as compared to established antibody responses. The clinical course was characterized by initial systemic symptoms and subsequent definite central neurological symptoms. This is specified in more detail in the Table, showing that the onset of symptoms was within the first 2 weeks (days 8–11) after vaccination. This is consistent with the data

TABLE. Overview of the Time Course of Systemic and Definite CNS Symptoms after ChAdOx1 nCoV-19 Vaccination

Patient #	Vaccination	Systemic Symptoms	Definite CNS Symptoms
1	First vaccination with ChAdOx1 nCoV-19, day 0	Day 1: fever and malaise Day 5: headache progressive disturbances of attention and concentration (possible but not definite CNS symptoms) Day 10: repulsive behavior	Day 10: confusion Day 11: evidence of pleocytosis in CSF
2	First vaccination with ChAdOx1 nCoV-19, day 0	Day 2: deep vein thrombosis of left leg Day 6: gait deterioration, vigilance disorder	Day 8: OMS Day 12: evidence of pleocytosis in CSF
3	First vaccination with ChAdOx1 nCoV-19, day 0	Day 8: fever	Day 8: aphasia Day 11: evidence of pleocytosis in CSF

All patients received the first vaccination with ChAdOx1 nCoV-19. This overview suggests that systemic symptoms occurred first, followed by definite CNS symptoms. Definite CNS symptoms occurred between days 8 and 11, which in our opinion is consistent with a possible postvaccinal reaction.
CNS = central nervous system; CSF = cerebrospinal fluid; OMS = opsoclonus–myoclonus syndrome.

we cited,[2] which provided a large database of postvaccinal encephalitis in which 50.7% of cases occurred within the first 2 weeks.

Recently, in a case series of patients with adverse events associated with various COVID-19 vaccinations, immune-mediated neurologic disorders including encephalitis were reported to occur with a median of 11 days following vaccination.[3] In the meantime, a case comparable to ours has been reported and attributed similarly.[4] Observations of other autoimmune central nervous system diseases such as acute disseminated encephalomyelitis (ADEM) after ChAdOx1 nCoV-19 vaccination are also consistent with our data.[5,6] Furthermore, these findings are supported by a review of the literature focusing on case reports of ADEM after vaccinations against various pathogens,[5,7] in which the average time between exposure to vaccines and the onset of symptoms ranged between 1 and 14 days.

We are aware that the immunological mechanism of postvaccination encephalitis is not fully understood. In the study by Ewer et al,[8] an unbiased approach was used to measure gross phenotypic and cellular changes at days 7, 14, and 28 after vaccination. Measurements before or shortly after day 7 were not performed. A multiplex cytokine analysis at day 7 after vaccination revealed increased secretion of interferon-γ and interleukin-2, indicating Th1 cytokine secretion in response to stimulation with SARS-CoV-2 spike peptides in subjects receiving the ChAdOx1 nCoV-19 vaccine. The cellular immune response showed discrete populations of T cells, natural killer cells, and B cells as early as 7 days after ChAdOx1 nCoV-19 vaccination. At all time points after vaccination, B cells, particularly the immunoglobulin G+ B-cell population, exhibited increased levels of Ki-67, a marker of increased cell proliferation, which in turn can be interpreted as an early immune response after vaccination.

Importantly, Dr Wiznitzer refers to an mRNA vaccine. However, our case series exclusively focused an adenovirus-vectored vaccine, which may impact the side effect potential as well as the immunological mechanisms postvaccination.

Regardless of established causalities, we believe that we are obliged as clinical neurologists to report potential complications of ChAdOx1 nCoV-19 vaccination, thus enabling an open discussion and timely diagnosis as well as treatment of similar cases. Despite established or presumed complications, we emphasize that the benefits of vaccination clearly outweigh its risks.

Potential Conflicts of interest

Nothing to report.

[1]*Department of Neurology, University Hospital OWL of the University Bielefeld, Campus Bielefeld-Bethel, Bielefeld, Germany*
[2]*Department of Neuroradiology, University Hospital OWL of the University Bielefeld, Campus Bielefeld-Bethel, Bielefeld, Germany*

References

1. Zuhorn F, Graf T, Klingebiel R, et al. Postvaccinal encephalitis after ChAdOx1 nCov-19. Ann Neurol 2021;90:506–511. Available at:. https://onlinelibrary.wiley.com/doi/full/10.1002/ana.26182.

2. Al Qudah Z, Abukwaik W, Patel H, Souayah N. Encephalitis after vaccination in United States. A report from the CDC/FDA vaccine adverse event reporting system [1990–2010] (P03.151). Neurology 2012;78.

3. Kaulen LD, Doubrovinskaia S, Mooshage C, et al. Neurological autoimmune diseases following vaccinations against SARS-CoV-2: a case series. Eur J Neurol 2022;29:555–563. Available at: https://

onlinelibrary.wiley.com/doi/full/10.1111/ene.15147. Accessed January 14, 2022.

4. Takata J, Durkin SM, Wong S, et al. A case report of ChAdOx1 nCoV-19 vaccine–associated encephalitis. BMC Neurol 2021;21:1–5. Available at: https://bmcneurol.biomedcentral.com/articles/10.1186/s12883-021-02517-w. Accessed January 14, 2022.

5. Permezel F, Borojevic B, Lau S, de Boer HH. Acute disseminated encephalomyelitis (ADEM) following recent Oxford/AstraZeneca COVID-19 vaccination. Forensic Sci Med Pathol 2021:1–6. Available at: https://pubmed.ncbi.nlm.nih.gov/34735684/. Accessed January 14, 2022.

6. Rinaldi V, Bellucci G, Romano A, et al. ADEM after ChAdOx1 nCoV-19 vaccine: a case report. Mult Scler J 2021. Available at: https://journals.sagepub.com/doi/10.1177/13524585211040222?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub++0pubmed. Accessed January 14, 2022.

7. Huynh W, Cordato DJ, Kehdi E, et al. Post-vaccination encephalomyelitis: literature review and illustrative case. J Clin Neurosci 2008;15:1315–1322. Available at: http://www.jocn-journal.com/article/S0967586808001896/fulltext. Accessed January 14, 2022.

8. Ewer KJ, Barrett JR, Belij-Rammerstorfer S, et al. T cell and antibody responses induced by a single dose of ChAdOx1 nCoV-19 (AZD1222) vaccine in a phase 1/2 clinical trial. Nat Med 2021;27:270–278.

DOI: 10.1002/ana.26314