Boffin Access
FOSTERING KNOWLEDGE

Open Access Journal | Volume: 3.1

Current Trends in Vaccines and Vaccinology

ISSN 2631-8970

Neurological Adverse Events Emerging in Covid-19 Vaccine Trial. Is Autoimmunity Involved?

Paolo Bellavite | Department of Medicine, Section of General Pathology, University of Verona (I), Italy

Summary

Some anecdotal reports of adverse events following vaccination with adenoviral vaccines related to neurological disorders. Although not considered causally related to the vaccine, the critical issue requires the utmost caution. In light of the fact that HEK293 cells, in which the vaccine adenoviruses are grown, are neuronal lineage, and that the virus spike protein has many homologies with human proteins, the possibility of a trigger of neurological autoimmune diseases cannot be ruled out in principle. Understanding this possibility could help to better inspect the antibody and lymphocyte reactions that are triggered by the vaccine, by measuring any autoantibodies against neuronal proteins in the serum of the volunteers.

Researchers and vaccine developers around the world are developing Coronavirus disease 2019 (COVID-19) vaccines and several candidate vaccines are now undergoing evaluation in clinical trials, although none had been approved for general use [1]. At least four of the candidate COVID-19 vaccines use replication-deficient adenoviruses cultivated on the line HEK-293, developed in the lab of molecular biologist Alex van der Eb at Leiden University [2]. The HEK293 kidney embryonal cell line was derived from the transformation of primary cultures of human embryonic kidney cells with adenovirus-5 (Ad5) DNA. Once transformed and cultured in the laboratory, these cells are widely used in research and industry and in the production of new generation vaccines, of which particularly current are those for immunization against Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [3-7]. An adenoviral vector grown on HEK293 is also currently being tested for immunization against tuberculosis [8].

Phase 2/3 trials have been started on healthy volunteers of these vaccine formulas and a few reports of neurological adverse reactions have emerged, the causal link of which with the vaccine cannot be established also because the cases are too few to be of statistical value. This interpretation difficulty is normal in phase 2 and 3 studies for particularly rare reactions. Since the reactions reported, including transverse myelitis, are particularly serious, they even generated a momentary halt to the experiment and alarmed the population. Some concerns have been raised regarding the lack of transparency in reporting the nature and number of such reactions in ongoing trials [9]. Pending the clarification of the causes of neurological diseases, we intend to point out the possibility that they are autoimmune reactions to some vaccine components and the biological plausibility of the phenomenon. Transverse myelitis occurrence after influenza vaccine and other virus vaccines was previously reported [10-16], but according to some authors the evidence for a causal association is inconclusive [17].

Although the HEK cell line is derived from kidney cells of a human embryo [2], subsequent evidence was provided that the transformed line with Ad5 insertion shares many characteristics of neuronal cells [18]. This study done with immunostaining, immunoblot and microarray analysis techniques showed that HEK293 cells develop neurofilaments (NF) and express NF-L, NF-M, NF-H subunits. Additionally, they found α-internexin as well as many other proteins typically found in neurons. Furthermore, other independently derived HEK lines from the originals, once transformed with adenoviruses (Ad5 and Ad12) express NF proteins, suggesting that similarity to neuronal cells is a common feature to cells transformed by adenovirus. This finding may suggest that these adenoviruses have a particular tropism for cells of neuronal lineage. For these reasons, others pointed out that these cells should not be used as kidney cells [19]. More recently, HEK293 cells were used as a model of neuronal cells expressing functional muscarinic receptors blocked by atropine [20].

These biological characteristics of HEK293 cells could generate the hypothesis

Article Information

DOI:	10.31021/CTVV.20203113
Article Type:	Letter to Editor
Journal Type:	Open Access
Volume:	3 **Issue:** 1
Manuscript ID:	CTVV-3-113
Publisher:	Boffin Access Limited
Received Date:	28 November 2020
Accepted Date:	15 December 2020
Published Date:	17 December 2020

*Corresponding author:

Paolo Bellavite
Department of Medicine
Section of General Pathology
University of Verona (I), Italy
Email: paolo.bellavite@univr.it

Citation: Bellavite P. Neurological Adverse Events Emerging in Covid-19 Vaccine Trial. Is Autoimmunity Involved? Curr Trends Vaccine Vaccinol. 2020 Dec;3(1):113

that some neurological events observed in people treated with recent coronavirus vaccines are actually autoimmune reactions against the residual substances of the neuron-like cells in which the vaccine viruses are grown. This hypothesis is corroborated by the recent observation that in neurological autoimmunity a correlation between disease activity and NF-L values was observed [21] and that anti-NF antibodies have been observed in various neurological diseases, correlating with progression [22]. Our hypothesis don't exclude that autoimmune reactions could be triggered by a cross-reaction with an adenovirus vector itself or with proteins coded by the RNA vaccine, since a noteworthy molecular mimicry has bees found between SARS-CoV-2 spike and human proteins [23]. To confirm or refute the risk of neurological autoimmune reactions, we suggest that sera from people treated with adenoviral COVID-19 vaccines are tested for the possible presence of antibodies against neuronal proteins.

References

1. Petersen E, Wejse C, Zumla A. Advancing COVID-19 vaccines â€“ avoiding different regulatory standards for different vaccines and need for open and transparent data sharing. Int J Infect Dis. 2020 Sep;98:501–502.
2. Graham FL, Smiley J, Russell WC, Nairn R. Characteristics of a human cell line transformed by DNA from human adenovirus type 5. J Gen Virol. 1977 Jul;36(1):59-74.
3. Feng L, Wang Q, Shan C, Yang C, Feng Y, et al. An adenovirus-vectored COVID-19 vaccine confers protection from SARS-COV-2 challenge in rhesus macaques. Nat Commun. 2020 Aug 21;11(1):4207.
4. Folegatti PM, Ewer KJ, Aley PK, Angus B, Becker S, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. Lancet. 2020 Aug;396(10249):467-478.
5. Ejemel M, Li Q, Hou S, Schiller ZA, Tree JA, et al. A cross-reactive human IgA monoclonal antibody blocks SARS-CoV-2 spike-ACE2 interaction. Nat Commun. 2020 Aug;11(1):4198.
6. Wu S, Zhong G, Zhang J, Shuai L, Zhang Z, et al. A single dose of an adenovirus-vectored vaccine provides protection against SARS-CoV-2 challenge. Nat Commun. 2020 Aug;11(1):4081.
7. Dai L, Zheng T, Xu K, Yuxuan H, Lili X, et al. A Universal Design of Betacoronavirus Vaccines against COVID-19, MERS, and SARS. Cell 2020 Aug;182(3):722-733.
8. Wilkie M, Satti I, Minhinnick A, Harris s, Riste M, et al. A phase I trial evaluating the safety and immunogenicity of a candidate tuberculosis vaccination regimen, ChAdOx1 85A prime - MVA85A boost in healthy UK adults. Vaccine. 2020 Jan;38(4):779-789.
9. Mallapaty S, Ledford H. COVID-vaccine results are on the way - and scientists' concerns are growing. Nature. 2020 Oct;586(7827):16-17.
10. Agmon-Levin N, Kivity S, Szyper-Kravitz M, Shoenfeld Y. Transverse myelitis and vaccines: a multi-analysis. Lupus 2009 Nov;18(13):1198-1204.
11. Menge T, Cree B, Saleh A, Waterboer T, Berthele A, et al. Neuromyelitis optica following human papillomavirus vaccination. Neurology. 2012 Jul;79(3):285-287.
12. Ussel IV, Boer W, Parizel P, Cras P, Jorens PG. Encephalitis related to a H1N1 vaccination: case report and review of the literature. Clin Neurol Neurosurg. 2014 Sep;124:8-15.
13. Austin A, Tincani A, Kivity S, Arango MT, Shoenfeld Y. Transverse Myelitis Activation Post-H1N1 Immunization: A Case of Adjuvant Induction? Isr Med Assoc J. 2015 Feb;17(2):120-122.
14. Rodriguez Y, Rojas M, Pacheco Y, Acosta-Ampudia Y, Ramírez-Santana C, et al. Guillain-Barré syndrome, transverse myelitis and infectious diseases. Cell Mol Immunol. 2018 Jun;15(6):547-562.
15. Bartol KD, Aguirre JL, Labruzzo SV, Henriet RP. Transverse myelitis associated with yellow fever vaccination. Proc (Bayl Univ Med Cent). 2019 Apr;32(2):283-285.
16. Cho JH, Park Y, Woo N. A case of neuromyelitis optica spectrum disorder following seasonal influenza vaccination. Mult Scler Relat Disord. 2019 May;30:110-113.
17. Baxter R, Lewis E, Goddard K, Fireman B, Bakshi N, et al. Acute Demyelinating Events Following Vaccines: A Case-Centered Analysis. Clin Infect Dis 2016 Dec;63(11):1456-1462.
18. Shaw G, Morse S, Ararat M, Graham FL. Preferential transformation of human neuronal cells by human adenoviruses and the origin of HEK 293 cells. FASEB J. 2002 Jun;16(8):869-871.
19. Toth K, Wold WS. HEK? No! Mol Ther 2002 Jun;5(6):654.
20. Morozova V, Cohen LS, Makki AE, Shur A, Pilar g, et al. Normal and Pathological Tau Uptake Mediated by M1/M3 Muscarinic Receptors Promotes Opposite Neuronal Changes. Front Cell Neurosci. 2019 Sep;13:403.
21. Mariotto S, Gajofatto A, Zuliani L, Zoccarato M, Gastaldi M, et al. Serum and CSF neurofilament light chain levels in antibody-mediated encephalitis. J Neurol 2019 Jul;266(7):1643-1648.
22. Zmira O, Halpern AI, Drori T. Anti-neurofilament antibodies and neurodegeneration: Markers and generators. J Neuroimmunol. 2020 Jul;344:577248.
23. Kanduc D, Shoenfeld Y. Molecular mimicry between SARS-CoV-2 spike glycoprotein and mammalian proteomes: implications for the vaccine. Immunol Res. 2020 Sep:1-4.