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LETTER TO THE EDITOR

Motor and non-motor symptom improvement after mRNA-1273 vaccine in a Parkinson's disease patient

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Dear Editor-in-Chief,

The coronavirus disease-2019 (Covid-19) has been causing more than 195 million cases of infection and 4 million deaths worldwide so far (https://covid19.who.int/). This ongoing global pandemic has urged the scientific community to promptly find new therapeutics and vaccines. Even though several neurological complications related to vaccine administration have been reported, global benefits outweigh the risks and the whole community of movement disorders specialists is encouraging Covid-19 vaccination [1]. The approved mRNA-based and viral vector vaccines are not known to interact with the neurodegenerative process in Parkinson's disease (PD), but two cases of severe dyskinesia after the BNT162b2 vaccine have been recently reported [2]. Conversely, we herein describe a PD patient who benefited from the administration of the mRNA-1273 vaccine. This 55-year-old gentleman, diagnosed with PD 6 years ago, was treated with 550 mg of levodopa-carbidopa/day divided into four doses and safinamide 100 mg/day, with partial control of the clinical picture due to persistent motor and non-motor wearing-off phenomena. He scored 7 points in the Non-Motor Fluctuation Assessment Questionnaire (NoMoFA), reporting severe painful/strange sensations and low energy levels in the off condition. The MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part IV score was 10, more in detail he had painful off dystonia and fluctuations with moderate impact on his daily activities and minimal dyskinesia. Apart from his neurological history, he suffered from hypertension and was treated with losartan and nebivolol. The first and second doses of the mRNA-1273 vaccine were respectively administered on May 28 and June 26. Right after the first shot, the patient reported global improvement of his motor and non-motor off symptoms, with greater efficacy on the most affected side (NoMoFA score = 4, 43% improvement; MDS-UPDRS part IV = 7, 30% improvement), and a sustained benefit for almost one week after the second shot. The reasons behind these beneficial effects are not easy to clarify, and similar cases have not been previously reported. Firstly, it should be highlighted that even though total CD4 + T cell responses are strongly biased towards the production of T helper 1 (Th1) cytokines in both the BNT162b2 and mRNA-1273 vaccines, no antigen-specific CD8 + T cell responses were found after immunization with mRNA-1273 in rhesus macaques during preclinical trials, even with high doses [3]. Therefore, the lack of an effective CD8 + T cell response could result in the reduction of cytotoxic T lymphocytes, interferon-γ- and interleukin-17, with blunted inflammatory activation. If on one hand, an increase in blood–brain barrier permeability could promote immune cell infiltration in the central nervous system [2], on the other, it could enhance the transport of levodopa and other potentially beneficial compounds into the brain. Our patient was also treated with losartan, an angiotensin type-1-receptor antagonist that crosses the blood–brain barrier and protects dopaminergic neurons against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) toxicity in primary ventral mesencephalic cultures and the substantia nigra pars compacta of C57BL/6 mice [4]. This benefit could be explained through the antagonism of the AT_1 receptors and the subsequent activation of the AT_2 receptors, which leads to the downregulation of NADPH oxidase and reduced oxidative stress [4]. Additionally, Reardon and colleagues found that perindopril, another

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renin-angiotensin system modulator, determined a faster response to levodopa and more "on" periods without peak dyskinesia in seven PD patients [5]. In addition to the crucial role exerted by the renin-angiotensin pathway in the perpetuation of neuroinflammatory mechanisms, in the present case, the fast onset and transient nature of the clinical benefit may more likely suggest a reversible immune-mediated change in blood–brain barrier permeability. These observations, though strongly speculative, highlight the variety of responses after Covid-19 vaccination and broaden the clinical spectrum of motor and non-motor effects in PD patients. Since the positive reaction appeared after both administrations with a tight temporal association and no other alternative causes could be identified, we believe the mRNA-1273 vaccine could have reasonably contributed to this outcome. Nonetheless, whether the key mechanisms are based on peculiar immunological properties of vaccine formulations or are influenced by other factors has yet to be fully understood.

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Declarations

Ethics approval and informed consent We confirm that we have read the Journal's position on issues involved in ethical publication and confirm that this work is consistent with those guidelines. The patient gave his written informed consent before the inclusion in the study. The approval of an institutional review board was not required for this work.

Conflict of interest The authors declare no competing interests.

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