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Interferon Beta-1b Level in Parkinson's Disease: Before and After SARS-CoV-2 Vaccination

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Abstract

Background: Parkinson's disease (PD) is a neurodegenerative disease. Immune response varies after vaccination in different patients. We aimed to evaluate interferon beta-1b (IFNβ-1b) level in patients with PD in response to inactivated SARS-CoV-2 (CoronaVac) vaccination.

Methods: Eight patients with the diagnosis of idiopathic PD and followed in the outpatient clinic (stages 1-2) were enrolled. Total blood count was performed before vaccination. IFNβ-1b levels were measured by ELISA and motor examination was performed before and two hours after vaccination.

Results: IFNβ-1b levels increased in three patients, whereas no change was detected in one patient and the levels decreased in four patients. Divergent responses were found related to the time of diagnosis.

Conclusion: The time of PD diagnosis, as well as the age of the patients, may be responsible for the variability of the post-vaccine immune response.

Keywords: Parkinson's disease; Interferon beta-1b; COVID-19; Vaccination; Immune response; Inflammation; Cytokine.

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Introduction

Parkinson's disease (PD) is a heterogeneous neurodegenerative disease and the most common form of Parkinsonism that affects 6 million individuals worldwide.[1] It is characterized by loss of dopaminergic neurons with a pathological hallmark of α-synuclein (α-syn) aggregates in Lewy bodies and neurites in particular in the ventral midbrain of patients with PD.[2] Microglia response in the cerebrum, as well as cellular and humoral peripheral immune response, are involved in PD, underlying the roles of both innate and adaptive immune systems.[3] Numerous studies reported altered levels of a variety of cytokines and chemokines including tumor necrosis factor (TNF), interleukin (IL)-1β, IL-6, IL-2, IL-10 in the blood, cerebrospinal fluid, and brain of patients with PD.[4] Moreover, genetic variations in immune-related genes such as TNFα, IL-6, and HLA genetic loci were shown to contribute to the complex pathogenesis of PD.[5,6]

While viral infections are not the primary cause of PD, they have been reported to be associated with increased risk of developing PD later in life.[7] Interferons (IFNs) are a broad class of cytokines and their response is essential for stimulation of the innate immune response during viral infection. IFN-β was proposed to have a protective role in PD by preventing dopaminergic neuron loss and inducing neuronal autophagy and α-syn clearance.[8] Moreover, IFN-β increased the microRNA (miR-1) expression in mammalian cells, which has a broad role in protection against the accumulation of aggregation-prone proteins.[9]

Hyperproduction of many other proinflammatory cytokines was also related to disease severity in patients with COVID-19.[10] A recent study focused on a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection of the brain, and proposed several pro-inflammatory cytokines such as TNF and IL-1β as responsible for the breakdown of the blood-brain barrier and an increased risk of PD.[11] In particular, recently, two studies demonstrated slightly altered gene expression of IFN-β also in patients with COVID-19.[12,13]

SARS-CoV-2 exerts neurological symptoms including impaired consciousness and hyposmia.[14] Though SARS-CoV-2 infections are not more frequent in patients with PD, a higher mortality rate has been observed. A recent review by Rosen and colleagues indicated that the interactions with the brain dopaminergic system and systemic inflammatory responses play roles in the higher mortality rate in patients with PD.[7]

COVID-19 vaccination is recommended for patients with PD by the experts unless there is a specific contraindication.[15] CoronaVac (Sinovac; Sinovac Life

Sciences, Beijing, China) is an inactivated and aluminium hydroxide adsorbed SARS-CoV-2 vaccine demonstrated to be safe with a low risk of severe adverse events and potent results.[16] We aimed to investigate the innate immune response and motor functions to CoronaVac vaccine in patients with PD by evaluating serum IFNβ-1b levels before and after the application of the vaccine.

Materials and Methods

Study Subjects

This prospective observational study was performed between 9/3/2021 and 9/4/2021 after obtaining the ethical approval. Patients followed in the outpatient clinic (stages 1-2 based on the Hoehn and Yahr staging system), with the diagnosis of PD were screened for the study. Inclusion criteria were idiopathic PD diagnosis and going to be vaccinated in the study center during the study period. Exclusion criteria were Parkinson Plus disorders, secondary parkinsonism, conditions which restrict removal blood such as anemia and coagulation disorders, and any other chronic disease affecting the immune system. Thirty-three patients with PD were screened for eligibility. Three of them had Parkinson plus, one of them had anemia, six had other system disorders and ten patients were going to be vaccinated in another healthcare setting. Ultimately, 13 patients were eligible and were vaccinated during the study period. Eight patients gave written informed consent to participate in the study.

Sociodemographic and Clinical Data

Age, sec, duration of PD (years), presence of comorbid diseases, family history for PD, and presence of a prior COVID-19 diagnosis were questioned prior to participation in the study.

Updated Unified Parkinson's Disease Rating Scale (UPDRS)

UPDRS part III (motor examination) evaluation consisting of 18 items was performed before and after the vaccination.[17]

Complete Blood Count

Blood was drawn to EDTA containing tubes. Complete blood count was performed before the vaccination on a CELL-DYN Ruby automated hematology analyzer (Abbott, USA) within 4 hours following drawing blood.

Evaluation of Interferon Beta-1b levels

Blood samples were allowed to clot for 2 hours at room temperature before centrifugation for 15 minutes at 1000 ×g. The supernatant was collected. Samples were aliquoted and stored at -20°C. Human Interferon Beta 1b ELISA Kit (BT Lab, China) was performed within one month according to the manufacturer's instructions to detect the IFNβ-1b levels in patients before and 2 hours after vaccination.

Statistical Analysis

Data are represented as mean ± standard deviation (SD). Paired *t* test and Wilcoxon test were used to compare paired samples. SPSS software, version 25, was used for analysis.

Results

Of the eight patients recruited, 50% were women. The mean ± SD age of the patients was 72.13± 6.75 years. The disease duration ranged from 1-20 years with a median of 5 years. Mean red blood cell (RBC), white blood cell (WBC) and mean platelet counts were 4.77×10^6/μL, 8.66×10^3/μL, and 249×10^3/μL, respectively. Mean lymphocyte count was 2.78×10^3 U/L (1.63-6.23) and the mean neutrophil count was 5.1×10^3/L (Table 1). The mean UPDRS motor scores before and after vaccination were 43.5 ± 36.2 (7-106) and 41.5 ± 33.5 (6-106), respectively (Table 2). UPDRS scores at the two-time points were comparable ($P > 0.05$). The mean IFNβ-1b level prior to vaccination was 10 ± 4 ng/L (5.91-19.6), which was measured as 14.3 ± 11 ng/L (4.88-40) two hours after vaccination ($P > 0.05$).

IFNβ-1b levels increased in three patients (patients 1, 2, and 4), whereas no change was observed in one patient and the levels decreased in four patients (patients 3, 5, 7,

Table 1. Age, Gender and Complete Blood Counts of the Patients

Patient (number)	Age (y)	Sex (Female/Male)	WBC (10^3/L)	RBC (10^6/L)	HGB (g/dL)	PLT (10^3/L)	LYMP (10^3/L)	NEUT (10^3/L)	EO (10^3/L)
1*	72	M	7.54	5.09	15.1	226	1.63	5.08	0.15
2	76	F	10.5	4.99	12.5	307	3.43	5.85	0.27
3	66	M	7.4	5.19	14.4	184	2.46	4.5	0.05
4	66	M	11.34	4.64	13.3	245	6.23	4.32	0.2
5**	64	F	7.14	4.17	11.3	284	2.02	4.59	0
6*	71	F	6.96	4.55	13.7	274	1.67	4.9	0.03
7	76	F	9.74	5.01	14.2	222	2.81	6.06	0.34
8	86	M	8.68	4.54	13.3	253	1.98	5.7	0.13

WBC, White Blood Cell; RBC, red blood cell; HGB, hemoglobin; PLT, platelet; LYMP, lymphocytes; NEUT, neutrophil; EO, eosinophil.
* Diagnosed as COVID-19 after vaccination.
** Hospitalized 9 months ago due to COVID-19.

Table 2. The Time of PD Diagnosis, UPDRS Motor Scores and IFNβ-1b Levels (Before and 2 Hours After Vaccination) of the Patients

Patient (number)	The time of PD Diagnosis (y)	UPDRS Motor Score (Before)	UPDRS Motor Score (After)	IFNβ-1b (ng/L, Before)	IFNβ-1b (ng/L, After)	Change in IFNβ-1b Level (%)
1 *	6	24	22	5.91	16.16	173↑
2	4	75	54	6.32	9.28	47↑
3	20	72	68	12.1	6.95	43↓
4	1	7	6	8.53	40	369↑
5**	4	9	9	11	9.82	11↓
6*	3	33	31	19.6	19.6	0
7	8	106	106	6.74	4.88	28↓
8	8	22	36	9.82	8.05	18↓

UPDRS, updated unified Parkinson's disease rating scale; IFNβ-1b, interferon beta-1b
* Diagnosed as COVID-19 after vaccination.
** Hospitalized 9 months ago due to COVID-19.

and 8). Patients 1 and 6 were COVID-19 positive by RT-PCR two days after screening (Tables 1 and 2). According to the national guidelines, patients were treated with Favipiravir for 5 days. They did not need hospitalization for the treatment. The level of IFNβ-1b increased in patient 1 but did not change in patient 6. Lymphocyte counts were in the lowest range in the mentioned patients.

The greatest decrease in IFNβ-1b level after 2 hours of vaccination was recorded in patient 3, a patient with young-onset PD who was currently receiving subthalamic stimulation and pharmacotherapy. The highest IFNβ-1b increase at the 2 h time-point was observed in patient 4. He was the patient with the shortest duration of PD, the lowest UPDRS score, and the highest lymphocyte counts. Patient 5 was a patient hospitalized 9 months ago because of COVID-19. In this patient, a decrease in IFNβ-1b level was detected after vaccination. Patient 7 was the patient with the most severe UPDRS score. In this patient, the post-vaccination IFNβ-1b level was low. In patient 8, these tests were performed after the rappel vaccine. This patient was the oldest patient. IFN levels decreased after vaccination.

Discussion

A viral infection initiates the inflammatory response by activation of a variety of signalling pathways and transcription factors which eventually lead to increased levels of the proinflammatory cytokines for recruitment of leukocytes and plasma proteins to the site of infection.[18] Innate immunity provides a rapid, nonspecific response to infection by the coordinated actions of multiple cells and facilitates adaptive immune responses.[19] IFNs constitute a family of cytokines that initiate the signalling pathways participating in both innate and adaptive immune responses against viruses and other pathogens.[20] Among those, type I IFN (IFN-I) is produced by a variety of cell types including macrophages, fibroblasts, endothelial cells, hepatocytes, microglia, and neurons, while hematopoietic cells were essential for an antiviral response.[21] IFNβ, an IFN-I with antiviral, immunomodulatory, and anti-tumor effects,[22] was also implicated in PD with a protective role against dopaminergic neuron loss and α-synuclein accumulation by increasing the microRNA miR-1expression.[8,9]

In the present study, we determined IFNβ-1b levels and UPDRS motor scores in patients with PD before and after the CoronaVac vaccination. We also assessed complete blood count. We demonstrated variable IFNβ-1b responses in the patients, pointing to different innate immunity responses. The patient with the shortest disease duration, lowest UPDRS score, and highest lymphocyte counts showed a dramatic increase in IFNβ-1b levels after vaccination (patient 4). On the other hand, the IFNβ-1b level halved 2 hours after vaccination in the patient with the longest duration of the disease (patient 3). In a patient diagnosed with COVID-19 two days after vaccination and with increased levels of IFNβ-lb in the second hour, adaptive immune responses might not have recognized the virus yet (patient 1). There were two limitations in this study, namely sample size and lack of homogeneity in PD severity. Anxiety disorders are common in patients with PD and pandemics are proposed to be a contributing factor to worsening anxiety mainly because of the restricted in-person visits.[23] Therefore, the small sample size and refusal to join the study could be explained by the alterations in hospital visits and increased anxiety level.

Conclusion

In our limited sample size, we observed an inverse relationship between the IFNβ-1b response and the duration of the disease. Similarly, we found that the IFNβ-1b levels inversely change with age. Vaccine responses are typically impaired in older individuals.[24] Further studies are required to investigate innate and adaptive immunity in chronic neurological diseases.

Conflict of Interest Disclosures

The authors declare that they have no conflict of interests.

Ethical Statement

This study was approved by the local clinical ethics board

of Maltepe University Faculty of Medicine, Istanbul (issue number:2021/900/37). A written, informed consent was obtained from all patients.

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References

1. Armstrong MJ, Okun MS. Diagnosis and treatment of Parkinson disease: a review. JAMA. 2020;323(6):548-60. doi: 10.1001/jama.2019.22360.
2. Kouli A, Torsney KM, Kuan WL. Parkinson's disease: etiology, neuropathology, and pathogenesis. In: Stoker TB, Greenland JC, eds. Parkinson's Disease: Pathogenesis and Clinical Aspects. Brisbane, AU: Codon Publications; 2018. doi: 10.15586/codonpublications.parkinsonsdisease.2018.ch1.
3. Tansey MG, Romero-Ramos M. Immune system responses in Parkinson's disease: early and dynamic. Eur J Neurosci. 2019;49(3):364-83. doi: 10.1111/ejn.14290.
4. Harms AS, Ferreira SA, Romero-Ramos M. Periphery and brain, innate and adaptive immunity in Parkinson's disease. Acta Neuropathol. 2021;141(4):527-45. doi: 10.1007/s00401-021-02268-5.
5. Chu K, Zhou X, Luo BY. Cytokine gene polymorphisms and Parkinson's disease: a meta-analysis. Can J Neurol Sci. 2012;39(1):58-64. doi: 10.1017/s0317167100012695.
6. Hamza TH, Zabetian CP, Tenesa A, Laederach A, Montimurro J, Yearout D, et al. Common genetic variation in the HLA region is associated with late-onset sporadic Parkinson's disease. Nat Genet. 2010;42(9):781-5. doi: 10.1038/ng.642.
7. Rosen B, Kurtishi A, Vazquez-Jimenez GR, Møller SG. The intersection of Parkinson's disease, viral infections, and COVID-19. Mol Neurobiol. 2021;58(9):4477-86. doi: 10.1007/s12035-021-02408-8 .
8. Ejlerskov P, Hultberg JG, Wang J, Carlsson R, Ambjørn M, Kuss M, et al. Lack of neuronal IFN-β-IFNAR causes Lewy body- and Parkinson's disease-like dementia. Cell. 2015;163(2):324-39. doi: 10.1016/j.cell.2015.08.069.
9. Nehammer C, Ejlerskov P, Gopal S, Handley A, Ng L, Moreira P, et al. Interferon-β-induced miR-1 alleviates toxic protein accumulation by controlling autophagy. Elife. 2019;8. doi: 10.7554/eLife.49930.
10. Costela-Ruiz VJ, Illescas-Montes R, Puerta-Puerta JM, Ruiz C, Melguizo-Rodríguez L. SARS-CoV-2 infection: the role of cytokines in COVID-19 disease. Cytokine Growth Factor Rev. 2020;54:62-75. doi: 10.1016/j.cytogfr.2020.06.001.
11. Sulzer D, Antonini A, Leta V, Nordvig A, Smeyne RJ, Goldman JE, et al. COVID-19 and possible links with Parkinson's disease and parkinsonism: from bench to bedside. NPJ Parkinsons Dis. 2020;6:18. doi: 10.1038/s41531-020-00123-0.
12. Salman AA, Waheed MH, Ali-Abdulsahib AA, Atwan ZW. Low type I interferon response in COVID-19 patients: interferon response may be a potential treatment for COVID-19. Biomed Rep. 2021;14(5):43. doi: 10.3892/br.2021.1419.
13. Contoli M, Papi A, Tomassetti L, Rizzo P, Vieceli Dalla Sega F, Fortini F, et al. Blood interferon-α levels and severity, outcomes, and inflammatory profiles in hospitalized COVID-19 patients. Front Immunol. 2021;12:648004. doi: 10.3389/fimmu.2021.648004.
14. Azhideh A, Menbari-Oskouie I, Yousefi-Asl M. Neurological manifestation of COVID-19: a literature review. Int Clin Neurosci J. 2020;7(4):164-70. doi: 10.34172/icnj.2020.20.
15. Bloem BR, Trenkwalder C, Sanchez-Ferro A, Kalia LV, Alcalay R, Chiang HL, et al. COVID-19 vaccination for persons with Parkinson's disease: light at the end of the tunnel? J Parkinsons Dis. 2021;11(1):3-8. doi: 10.3233/jpd-212573.
16. Doroftei B, Ciobica A, Ilie OD, Maftei R, Ilea C. Mini-review discussing the reliability and efficiency of COVID-19 vaccines. Diagnostics (Basel). 2021;11(4):579. doi: 10.3390/diagnostics11040579.
17. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord. 2008;23(15):2129-70. doi: 10.1002/mds.22340.
18. Ragab D, Salah Eldin H, Taeimah M, Khattab R, Salem R. The COVID-19 cytokine storm; what we know so far. Front Immunol. 2020;11:1446. doi: 10.3389/fimmu.2020.01446.
19. Rivera A, Siracusa MC, Yap GS, Gause WC. Innate cell communication kick-starts pathogen-specific immunity. Nat Immunol. 2016;17(4):356-63. doi: 10.1038/ni.3375.
20. Walter MR. The role of structure in the biology of interferon signaling. Front Immunol. 2020;11:606489. doi: 10.3389/fimmu.2020.606489.
21. Lang PA, Cervantes-Barragan L, Verschoor A, Navarini AA, Recher M, Pellegrini M, et al. Hematopoietic cell-derived interferon controls viral replication and virus-induced disease. Blood. 2009;113(5):1045-52. doi: 10.1182/blood-2007-10-117861.
22. Fox LE, Locke MC, Lenschow DJ. Context is key: delineating the unique functions of IFNα and IFNβ in disease. Front Immunol. 2020;11:606874. doi: 10.3389/fimmu.2020.606874.
23. Suran M. How prolonged isolation affects people with Parkinson disease during the COVID-19 Pandemic. JAMA. 2022;327(9):801-3. doi: 10.1001/jama.2022.1510.
24. Weyand CM, Goronzy JJ. Aging of the immune system. Mechanisms and therapeutic targets. Ann Am Thorac Soc. 2016;13(Suppl 5):S422-S8. doi: 10.1513/AnnalsATS.201602-095AW.