Lower Circulating Lymphocyte Count Predicts ApoE ε4-Related Cognitive Decline in Parkinson's Disease

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CITATION:

ISSUE DATE:
2021-12

URL:
http://hdl.handle.net/2433/266630

RIGHT:
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In conclusion, this study yields first evidence from longitudinal data of individual patients for the potential of iron and ferritin as progression marker in PD. A validation of our findings in a larger cohort, more advanced PD patients and a longer follow-up period is warranted.

Acknowledgments: We gratefully appreciate the participation of our patients in this study. We thank our Parkinson’s and study nurses Gudrun Leyerer and Jennifer Heinemann for their excellent assistance. We also thank Peter Lange for providing helpful advice on assay-related issues. Open Access funding enabled and organized by Projekt DEAL.

Data Availability Statement

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

References


Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site.

Lower Circulating Lymphocyte Count Predicts ApoE ε4-Related Cognitive Decline in Parkinson’s Disease

Neuroinflammatory changes in the brain, including infiltration of lymphocytes, particularly T cells, play a critical role in the pathogenesis of Parkinson’s disease (PD). Interestingly, in the peripheral blood of PD patients, a decrease in circulating lymphocyte counts occurs, mainly due to a decrease in T cells. Furthermore, it has recently been reported that lower lymphocyte count might be causally related to the subsequent development of PD. Inspired by these observations, we aimed at assessing whether low lymphocyte count is associated with the subsequent development of the key milestones in PD’s disease course, specifically cognitive impairment, with a particular attention to the apolipoprotein E (ApoE) ε4 allele, a crucial modifying factor in cognitive impairment.

In this retrospective cohort study, using the Parkinson’s Progression Markers Initiative data, 167 de novo PD patients were enrolled (Fig S1) and followed up for 2 years (Tables S1 and S2; Text S1). R scripts made for the analysis are freely available at http://dx.doi.org/10.17632/7s8ng9yn8.2 or https://github.com/KazutoTsukita/Mov_Disord_2021.

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Relevant conflicts of interest/financial disclosures: Nothing to report.

Funding agency: Nothing to report.

Received: 13 August 2021; Accepted: 26 August 2021

Published online 13 October 2021 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.28799
We primarily used the multivariate linear mixed-effects model adjusted for various covariates (age, sex, levodopa-equivalent dose, disease duration, and baseline severity of smell deficit and rapid-eye-movement sleep behavior). We observed that only in PD patients carrying ApoE ε4 allele, baseline lymphocyte count had significant interaction effect on the longitudinal decline in the Montreal Cognitive Assessment (MoCA) total score, such that lower baseline lymphocyte count was associated with accelerated MoCA score decline (carrier, the standardized fixed-effects coefficient of the interaction term (βinteraction) = 0.17 [95% confidence interval, CI: 0.04, 0.30], P = 0.01; noncarrier, βinteraction = −0.00 [95% CI: −0.10, 0.09], P = 0.94). When PD patients, with and without ApoE ε4 allele, were dichotomized using the median of baseline lymphocyte count (carrier, 1.72 × 10^7/μL; noncarrier, 1.74 × 10^7/μL) (Table S3), the interaction effect was apparent only in PD patients carrying ApoE ε4 allele (carrier, βinteraction = 0.45 [95% CI: 0.20, 0.71], P < 0.001; noncarrier, βinteraction = −0.03 [95% CI: −0.22, 0.15], P = 0.72) (Fig. 1A,B). The interaction effects of baseline lymphocyte count on the progression of specific domains of cognitive impairment did not reach statistical significance (Fig. 1C). Sensitivity analyses confirmed the robustness of our result in a range of follow-up periods (Table S4) and even when missing values were imputed (Table S5).

An interesting aspect of the present result is that baseline lymphocyte count was clearly associated with subsequent cognitive decline only in PD patients carrying ApoE ε4 allele. Given the importance of ApoE ε4 allele in blood–brain barrier (BBB) dysfunction and the role of circulating T cells in PD pathogenesis (Text S2),1,7 our result might indicate the cooperative pathological role of BBB dysfunction and circulating lymphocytes in PD. Alternatively, the brain cortex of patients carrying ApoE ε4 allele may be particularly vulnerable to lymphocyte infiltration. Admittedly, this study has some limitations (Text S3); however, because many covariates were adjusted for, we believe that our result indicates that biological phenomenon reflected by the decrease in the lymphocyte count might actively exacerbate the pathology driving cognitive dysfunction in synergy with the ApoE ε4 allele, thereby providing important clinical and pathophysiological implications.

Acknowledgments: This work was supported by JST [Moonshot R&D] [Grant Number JPMJMS2024]. PPMI—a public–private partnership—is funded by the Michael J. Fox Foundation for Parkinson’s Research funding partners—4D Pharma, AbbVie, Acurex Therapeutics, Allergan, Amathus Therapeutics, ASAP, Avid Radiopharmaceuticals, Bial Biotech, Biogen, BioLegend, Bristol-Myers Squibb, Calico, Celgene, Dacapo Brain Science, Denali, the Edmond J. Safra Foundation, GE Healthcare, Genentech, GlaxoSmithKline, Golub Capital, Handl Therapeutics, Insitro, Jansen Neuroscience, Lilly, Lundbeck, Merck, Mesol Scale Discovery, Neurocine Biosciences, Pfizer, Piramal, Preval, Roche, Sanofi Genzyme, Servier, Takeda, Teva, UCB, Verily, and Voyager Therapeutics. We thank Dr. Takahiro Kamada for inspiring us to do this study. He died in January 2019, and we wish to dedicate this article in his memory.

Data Availability Statement

Data used in this retrospective cohort study were obtained from the Parkinson’s Progression Markers Initiative (PPMI) database (www.ppmi-info.org/data) on July 28, 2021. For up-to-date information on the study, visit www.ppmi-info.org. R scripts made for the analysis are freely available at http://dx.doi.org/10.17632/7s8sng9yn8.2. or https://github.com/KazutoTsukita/Mov_Distord_2021.

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References

Screening of GBA Mutations in Nigerian Patients with Parkinson’s Disease

Heterozygous mutations in the β-glucocerebrosidase (GBA) gene are reported in 5% to 30% of patients with Parkinson’s disease (PD) across White and Asian populations with a relative absence of studies in other populations.1,2 Nigeria is the most populated African country and has more than 5 million people who are aged older than 65 years.3 To date, the only GBA screening reported in Sub-Saharan Africa populations was performed in Black South African patients4; two novel missense variants (p.F216L and p.G477R) and three previously described (p.K(−27) R, p.T36del, and p.Q497*) variants were identified in 30 patients with PD.4 The aim of this study was to assess the frequency of GBA mutations in a series of Nigerian patients with PD and controls by gene sequencing.

Supporting Data

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Relevant conflicts of interest/financial disclosures: Mayo Clinic is an American Parkinson Disease Association (APDA) Mayo Clinic Information and Referral Center, an APDA Center for Advanced Research, and the Mayo Clinic Lewy Body Dementia Association Research Center of Excellence. L.M.M. is supported by the Polish National Agency for Academic Exchange Iwanowska’s Fellowship PPN/IWA/2018/1/000096/ U/00001/01. Z.K.W. is partially supported by the Mayo Clinic Center for Regenerative Medicine, Mayo Clinic in Florida Focused Research Team Program, the gifts from The Sol Goldman Charitable Trust, the Donald G. and Jodi P. Heeringa Family, the Haworth Family Professorship in Neurodegenerative Diseases fund, and The Albertson Parkinson’s Research Foundation. He serves as principal investigator or co-principal investigator on Biohaven Pharmaceuticals, Inc. (BH4157-206 and BHV3241-301) and NeuraLy, Inc. (NLV01-PD-1) grants and as external advisory board member for the Vigil Neuroscience, Inc. He serves as co-principal investigator of the Mayo Clinic APDA Center for Advanced Research.

Received: 10 August 2021; Revised: 27 August 2021; Accepted: 30 August 2021

Published online 29 September 2021 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.28803