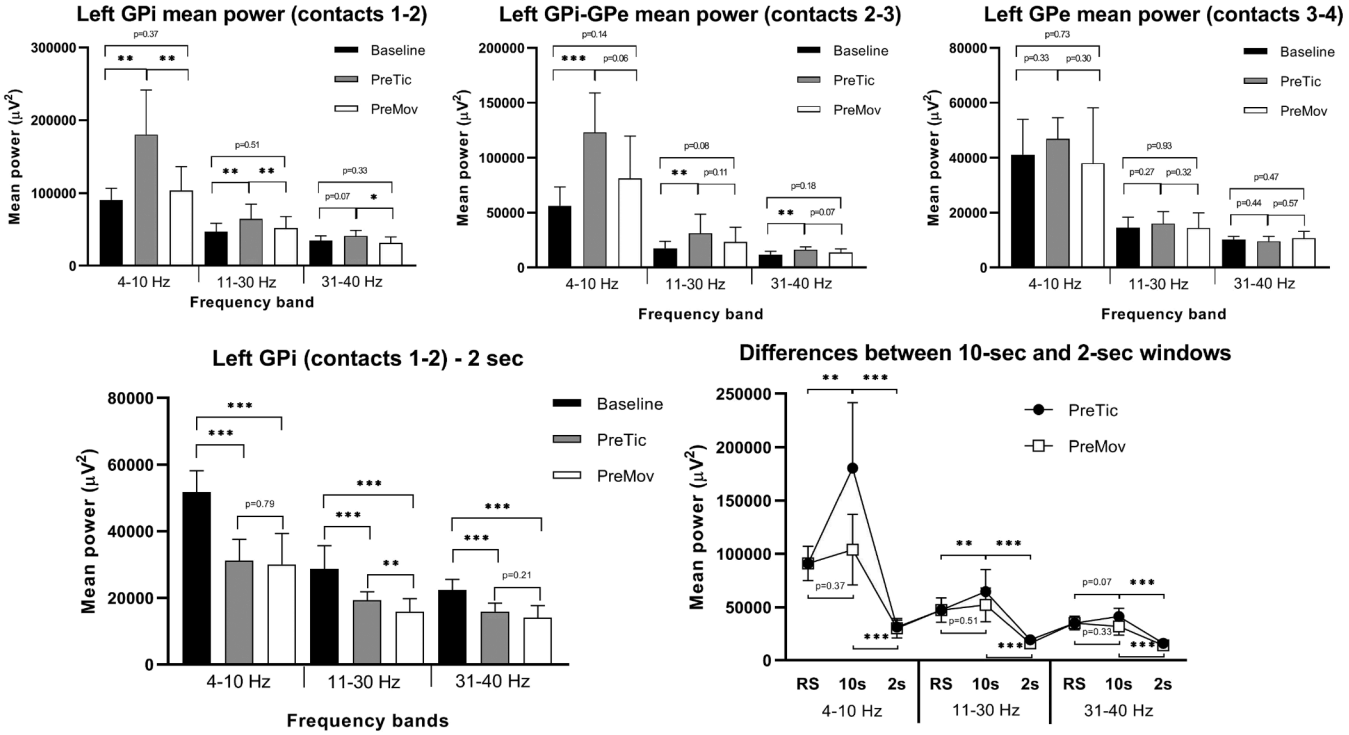

FIG. 1. Top row: mean power comparison between conditions in each pair of contacts is shown. A robust 4- to 10-Hz peak is observed in the 10 seconds before tic, which is not present in pre-movement and baseline recordings. This peak decreases as the distance from GPi increases. Lower left panel: mean power differences between baseline (resting state), pre-tic, and pre-movement activity in the different frequency bands during the 2-second period before movement/tic. During this period, there is a decrease in activity in all frequency bands. Pre-movement activity shows a steeper decrease in beta-band activity as compared with pre-tic activity, which suggests impaired/diminished motor processing. Low-frequency peaks are not observed preceding tic onset in this time segment. Lower right panel: differences between the 10-second and 2-second windows are shown. The most remarkable difference is the low-frequency peak in the 10-second window, which disappears in the 2 seconds before tic. Moreover, a beta-band decrease is observed in both conditions, reaching slightly lower levels before voluntary movements. Asterisks show the level of statistical significance: (*) = $p < 0.05$; (**) = $p < 0.01$; (***) = $p < 0.001$.

References

1. Brandt VC, Beck C, Sajin V, et al. Temporal relationship between premonitory urges and tics in Gilles de la Tourette syndrome. Cortex 2016;77:24–37.
2. Bohlhalter S, Goldfine A, Matteson S, et al. Neural correlates of tic generation in Tourette syndrome: an event-related functional MRI study. Brain 2006;129(Pt 8):2029–2037. https://doi.org/10.1093/brain/awl050
3. Neumann WJ, Huebl J, Brücke C, et al. Pallidal and thalamic neural oscillatory patterns in Tourette's syndrome. Ann Neurol 2018 Oct; 84(4):505–514. https://doi.org/10.1002/ana.25311
4. Jimenez-Shahed J, Telkes I, Viswanathan A, Ince NF. GPi oscillatory activity differentiates tics from the resting state, voluntary movements, and the unmedicated Parkinsonian state. Front Neurosci 2016;10:436. https://doi.org/10.3389/fnins.2016.00436
5. Cagle JN, Okun MS, Opri E, et al. Differentiating tic electrophysiology from voluntary movement in the human thalamocortical circuit. J Neurol Neurosurg Psychiatry 2020;91(5):533–539. https://doi.org/10.1136/jnnp-2019-321973

Supporting Data

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

Cerebrospinal Fluid Iron-Ferritin Ratio as a Potential Progression Marker for Parkinson's Disease

Biomarkers as surrogates for disease progression and drug response are urgently needed for Parkinson's disease (PD). In PD patients' brains, iron was shown to preferentially accumulate in

© 2021 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

***Correspondence to:** Dr. Fabian Maass, Department of Neurology, University Medical Center Göttingen, Robert-Koch-Str. 40, DE-37075 Göttingen, Germany; E-mail: fabian.maass@med.uni-goettingen.de

Relevant conflicts of interest/financial disclosures: None of the authors have anything to disclose regarding this manuscript.

Funding agencies: This study was funded by DFG Research Center for Nanoscale Microscopy and Molecular Physiology of the Brain (CNMPB) (P.L., M.B.); Forschungskolleg TRANSMED Göttingen, which was supported by the Ministerium für Wissenschaft und Kultur, Niedersachsen, Germany (F.M.).

Received: 26 July 2021; **Revised:** 25 August 2021; **Accepted:** 26 August 2021

Published online 23 September 2021 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.28790

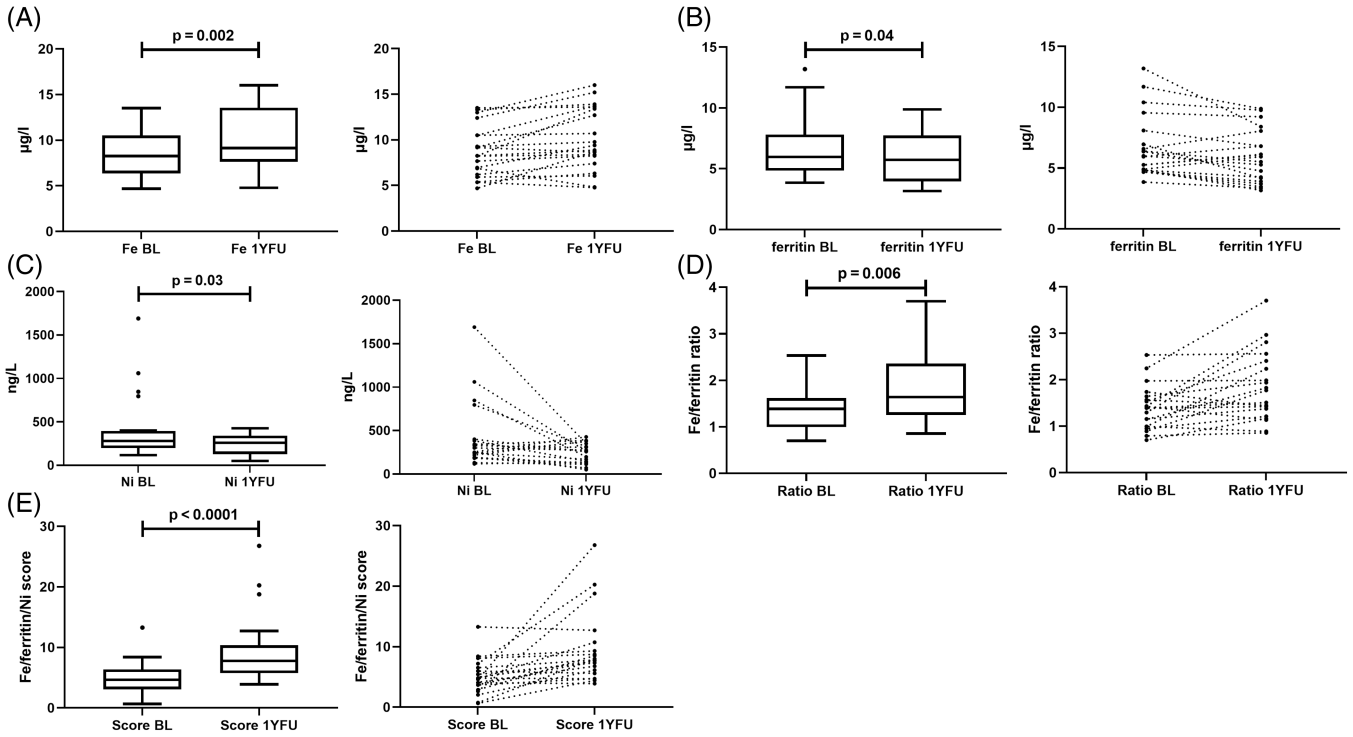

FIG. 1. Longitudinal evolution of iron, nickel, and ferritin in the cerebrospinal fluid of Parkinson's disease patients. Data are presented as boxplot [median, interquartile range (IQR), whiskers and outliers according to Tukey's rule] and as individual values, visualizing baseline, and follow-up quantification after 1 year for each individual patient. *P*-values were calculated according to Wilcoxon matched pairs signed rank test. (**A**) iron, (**B**) ferritin, (**C**) nickel, (**D**) iron/ferritin ratio, (**E**) iron/ferritin/nickel score, BL, baseline examination; 1YFU, follow-up examination after 1 year. The iron/ferritin/nickel score was defined as [Fe (µg/L)/(Ni (ng/L)) × ferritin (µg/L) × 1000].

the substantia nigra, and this accumulation increased over the disease course.[1,2] Iron accumulation has also been demonstrated in-vivo applying QSM-MRI.[3] On the contrary, levels of the iron-binding protein ferritin were reduced in almost all evaluated brain regions in PD patients.[4] In neurons, iron is mainly neuromelanin-bound, whereas ferritin-bound iron is more abundant in glia.[5] We hypothesized that longitudinal assessment of total cerebrospinal fluid (CSF) iron and ferritin levels could be used to reflect progressive brain iron dyshomeostasis and disease progression in individual PD patients.

For the first time, we report on a longitudinal CSF analysis of iron, ferritin, and additional bioactive elements (arsenic [As], copper [Cu], magnesium [Mg], nickel [Ni], selenium [Se], strontium [Sr], zinc [Zn]) with an implication in PD pathogenesis.[6-9] In addition, several protein markers of neurodegeneration were quantified.

Baseline and 1-year follow-up CSF samples of 20 PD patients were subjected to bioelement determination by mass-spectrometry [inductively coupled plasma optical emission spectrometry (ICP-OES), inductively coupled plasma-sector field mass spectrometry (ICP-sf-MS)].[10] Nephelometric analysis was used for ferritin quantification. Amyloid beta 1–40/1–42, total-tau, and phospho-tau were quantified using ELISA and alpha-synuclein using SIMOA techniques (see Supplementary Material). Wilcoxon matched pairs signed-rank test was used to evaluate longitudinal differences, and correlation analysis was performed using Spearman's rho. A permission of the local ethics committee was obtained, and written consent was provided by all patients or care givers.

In line with our main hypothesis, we report an increase in total iron over time ($P = 0.002$) while levels of ferritin decreased ($P = 0.04$). Levels of nickel also showed a significant decrease ($P = 0.03$). Application of an iron/ferritin ratio or an iron/ferritin/nickel score showed even more pronounced changes ($P = 0.006$; $P = <0.0001$, respectively; Fig. 1). All other bioelements and neurodegeneration markers remained stable over 1 year.

To exclude influences by the antiparkinsonian medication, a correlation analysis was performed, which revealed no association between changes in the levodopa equivalent dose (LED) and the changes in iron, ferritin, and nickel levels over time ($P > 0.05$).

Interestingly, there was a highly significant and strong correlation between baseline iron and baseline alpha-synuclein levels ($r = 0.78$, $P < 0.0001$, Supplementary Figure S1). Although this might reflect the metal binding affinity of alpha-synuclein, both might also be independently regulated in the course of disease. There was no correlation between baseline ferritin and alpha-synuclein levels after adjusting for multiple testing (see Supplementary Material).

Due to a compensation by a significant increase in LED ($P = 0.0003$), no significant worsening in motor, nonmotor, and cognitive scores could be detected at the 1-year follow-up ($P > 0.05$) in our cohort, which mainly included early-stage PD patients. Therefore, correlation analyses between changes in CSF parameters and changes in clinical parameters were not applicable. As a limitation of this study, we therefore cannot establish a direct association of iron and ferritin levels to motor and nonmotor scores.

15318257, 2021, 12, Downloaded from https://movementdisorders.onlinelibrary.wiley.com/doi/10.1002/mds.28790 by Deutsches Zentrum Für Neurodeg, Wiley Online Library on [24/04/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

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.

Fabian Maass, MD,[1*] Bernhard Michalke, PhD,[2] Desiree Willkommen, (Ms.),[2] Sezgi Canaslan, (Ms.),[1] Matthias Schmitz, PhD,[1,3] Mathias Bähr, MD,[1,4] Inga Zerr, MD,[1,3] and Paul Lingor, MD[5,6]

[1]*Department of Neurology, University Medical Center Göttingen, Goettingen, Germany,* [2]*Research Unit Analytical BioGeoChemistry, German Research Center for Environmental Health, Helmholtz Zentrum München, Neuherberg, Germany,* [3]*DZNE, German Center for Neurodegenerative Diseases, Goettingen, Germany,* [4]*Center for Biostructural Imaging of Neurodegeneration (BIN), University of Göttingen Medical Center, Göttingen, Germany,* [5]*Department of Neurology, School of Medicine, Klinikum rechts der Isar, Technical University of Munich, München, Germany, and* [6]*DZNE, German Center for Neurodegenerative Diseases, Munich, Germany*

References

1. Ward RJ, Zucca FA, Duyn JH, Crichton RR, Zecca L. The role of iron in brain ageing and neurodegenerative disorders. Lancet Neurol 2014;13(10):1045–1060. https://doi.org/10.1016/S1474-4422(14)70117-6
2. Dexter DT, Wells FR, Lee AJ, et al. Increased nigral iron content and alterations in other metal ions occurring in brain in Parkinson's disease. J Neurochem 1989;52(6):1830–1836. https://doi.org/10.1111/j.1471-4159.1989.tb07264.x
3. Acosta-Cabronero J, Cardenas-Blanco A, Betts MJ, et al. The whole-brain pattern of magnetic susceptibility perturbations in Parkinson's disease. Brain 2016;140(2016):aww278. https://doi.org/10.1093/brain/aww278
4. Dexter DT, Carayon A, Javoy-agid F, et al. Alterations in the levels of iron, ferritin and other trace metals in parkinson's disease and other neurodegenerative diseases affecting the basal ganglia. Brain 1991;114:1953–1975. https://doi.org/10.1093/brain/114.4.1953
5. Zecca L, Stroppolo A, Gatti A, et al. The role of iron and molecules in the neuronal vulnerability of locus coeruleus and substantia nigra during aging. Proc Natl Acad Sci U S A 2004;101(26):9843–9848. https://doi.org/10.1073/pnas.0403495101
6. Cholanians AB, Phan AV, Ditzel EJ, Camenisch TD, Lau SS, Monks TJ. Arsenic induces accumulation of α-synuclein: implications for synucleinopathies and neurodegeneration. Toxicol Sci 2016;153(2):271–281. https://doi.org/10.1093/toxsci/kfw117
7. Sun H. Association of soil selenium, strontium, and magnesium concentrations with Parkinson's disease mortality rates in the USA. Environ Geochem Health 2018;40(1):349–357. https://doi.org/10.1007/s10653-017-9915-8
8. Davies KM, Bohic S, Carmona A, et al. Copper pathology in vulnerable brain regions in Parkinson's disease. Neurobiol Aging 2014;35(4):858–866. https://doi.org/10.1016/j.neurobiolaging.2013.09.034
9. Lucio M, Willkommen D, Schroeter M, Sigaroudi A, Schmitt-Kopplin P, Michalke B. Integrative metabolomic and metallomic analysis in a case–control cohort with Parkinson's disease. Front Aging Neurosci 2019;11:331. https://doi.org/10.3389/fnagi.2019.00331
10. Maass F, Michalke B, Willkommen D, et al. Elemental fingerprint: reassessment of a cerebrospinal fluid biomarker for Parkinson's disease. Neurobiol Dis 2020;134:104677. https://doi.org/10.1016/j.nbd.2019.104677

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).[1,2] Interestingly, in the peripheral blood of PD patients, a decrease in circulating lymphocyte counts occurs, mainly due to a decrease in T cells.[1,3] Furthermore, it has recently been reported that lower lymphocyte count might be causally related to the subsequent development of PD.[4] 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.[5,6]

In this retrospective cohort study, using the Parkinson's Progression Markers Initiative data, 167 de novo PD patients were enrolled (Fig. S1) and were 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/10.17632/7s8sng9yn8.2 or https://github.com/KazutoTsukita/Mov_Disord_2021.

© 2021 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

***Correspondence to:** Dr Kazuto Tsukita, Department of Neurology, Graduate School of Medicine, Kyoto University, 54 Shogoin-Kawaharacho, Kyoto 606-8507, Japan; E-mail: kazusan@kuhp.kyoto-u.ac.jp

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

15318257, 2021, 12, Downloaded from https://movementdisorders.onlinelibrary.wiley.com/doi/10.1002/mds.28790 by Deutsches Zentrum Für Neurodeg, Wiley Online Library on [24/04/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License