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 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

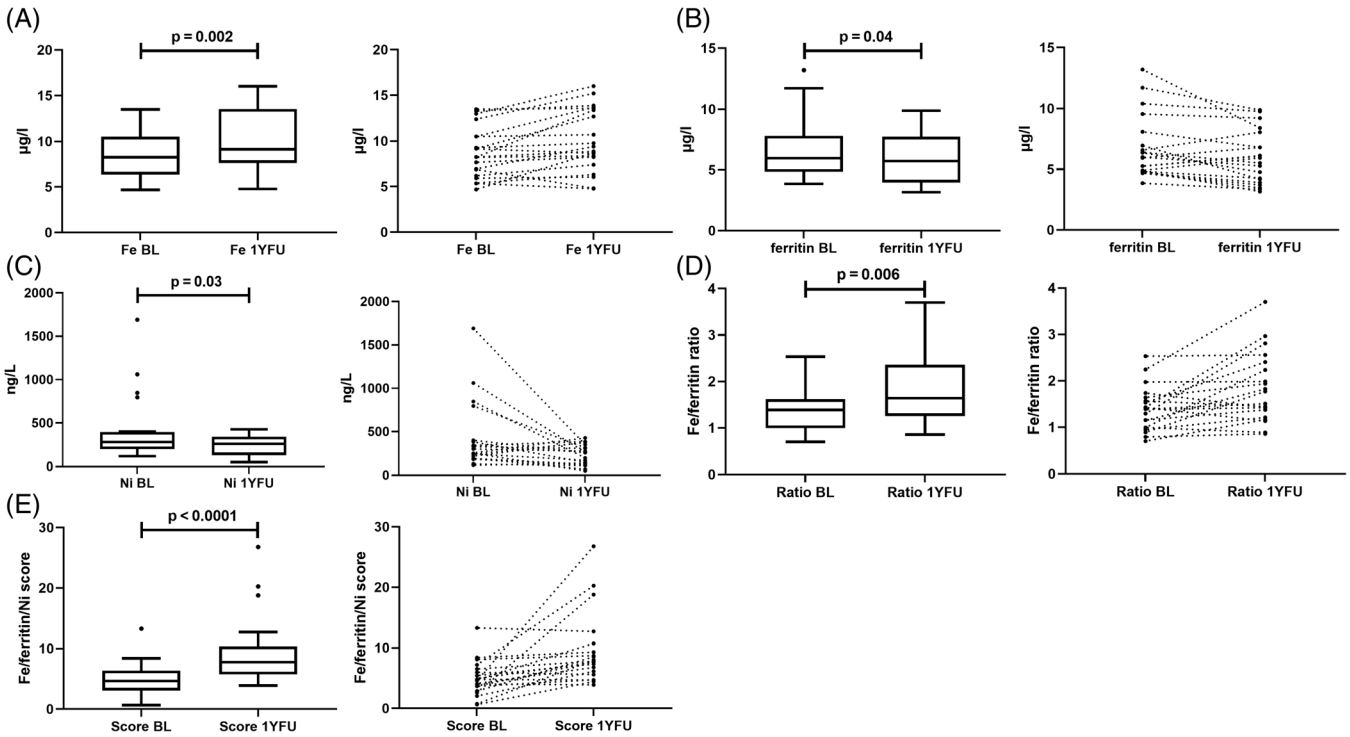

FIG. 1. Longitudinal evolution of iron, nickel, and ferritin in the cerebrospinal fluid of Parkinson's disease patients. Data are presented as boxplot [median, interquartile range (IQR), whiskers and outliers according to Tukey's rule] and as individual values, visualizing baseline, and follow-up quantification 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].

*__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

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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.

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.

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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*

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Supporting Data

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

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Author Roles

Design, conceptualization, and execution of the study: F.M., B.M., D.W., S.C., M.S., M.B., I.Z., P.L./Design, execution, and interpretation of the biostatistical analysis: F.M., P.L./Drafting the manuscript: F.M., P.L./Revising the manuscript: F.M., B.M., D.W., S.C., M.S., M.B., I.Z., P.L. All authors read and approved the final manuscript.

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