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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.

Validation of Plasma Neurofilament Light Chain as a Marker for α-Synucleinopathies

α-Synucleinopathies are a group of neurological disorders including Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). Due to clinical overlaps, accurate discrimination between different types of α-synucleinopathies is challenging. In addition, there is a lack of diagnostic markers in less-invasive body fluids, such as plasma, in this group of diseases.

A previous study already analyzed neurofilament light chain (NfL) levels in the cerebrospinal fluid (CSF) of α-synucleinopathies. Holmberg et al[1] reported elevated NfL levels in CSF from patients with MSA compared with patients with PD, suggesting NfL as a potential CSF marker for reflecting neuronal/axonal damage in α-synucleinopathies. A meta-analysis of 9 studies about CSF NfL levels in patients with MSA reported an increase of NfL levels in patients with MSA compared with patients with PD, suggesting NfL as a potential marker to distinguish between these 2 diagnoses.[2]

Our aim in the present study was the analysis of NfL concentrations in plasma of different types of α-synucleinopathies by using an ultrasensitive detection system, single molecule array (SIMOA).

We subjected plasma samples from patients with PD, DLB, and MSA (for clinical data, see Table S1) to SIMOA assay analysis (Supplementary Material). Measurement of NfL levels in plasma revealed that patients with DLB and MSA contained a significantly higher amount of NfL compared with patients with PD or the control group (Fig. 1A). To determine the diagnostic accuracy of plasma NfL, we combined the DLB and MSA groups (non-PD synucleinopathies) and conducted receiver operating characteristic (ROC) curve analyses using the *Graph Pad Prism 6.0.1* software. We grouped patients with DLB and MSA to obtain statistically more powerful values (Supplementary Material).

Interestingly, ROC curve analysis suggested plasma NfL with area under the curve (AUC) values between 0.88 and 0.90 ($P < 0.0001$) as a promising marker to distinguish between non-PD synucleinopathies and PD as well as between non-PD synucleinopathies and controls (Fig. 1B,C). Splitting of non-PD synucleinopathies into DLB and MSA (lower accuracy because of lower numbers per group) resulted in AUCs of 0.88 to 0.89 for DLB and slightly higher AUCs of 0.91 to 0.92 for MSA (Fig. S1A–D).

Until now, there are only few studies that investigated NfL levels in the plasma of α-synucleinopathies by using ultrasensitive detection systems (Table S2). A total of 2 studies observed an increased NfL level in patients with MSA compared with patients with PD and controls by using a SIMOA-based homebrew assay,[3,4] but samples from patients with DLB were not included. Depending on the cohort, Hansson et al[3] obtained AUC values between AUC 0.8 and 0.9 to distinguish between MSA and PD, which are comparable with our NfL data. Interestingly, we additionally identified elevated plasma NfL levels in patients with DLB that are not distinguishable from patients with MSA.

A limitation of this analysis is the relatively small number of available DLB and MSA cases that impeded a proper calculation of diagnostic accuracy. Therefore, a confirmation of our observations in larger cohorts is required.

In conclusion, our study suggests plasma NfL as a potential diagnostic marker to discriminate non-PD synucleinopathies from patients with PD and controls, which has prognostic and therapeutic value for these patients.

Ethics Approval

The study has been approved by local ethic committee of the University Medicine Göttingen: No. 19/11/09 "Liquormarker als Prädiktoren für die Entwicklung einer Demenz bei Patienten mit Morbus Parkinson, Demenz mit Lewy-Körperchen und Morbus Alzheimer" and No. 13/11/12 "LIX–Liquormarker zur Frühdiagnose und Krankheitsprogression bei Patienten mit Parkinson-Syndromen und Motorneuronerkrankungen."

Consent for Publication

All authors have read the manuscript and have indicated consent for publication.

Key Words: α-synucleinopathies; biomarker; neurofilament light chain

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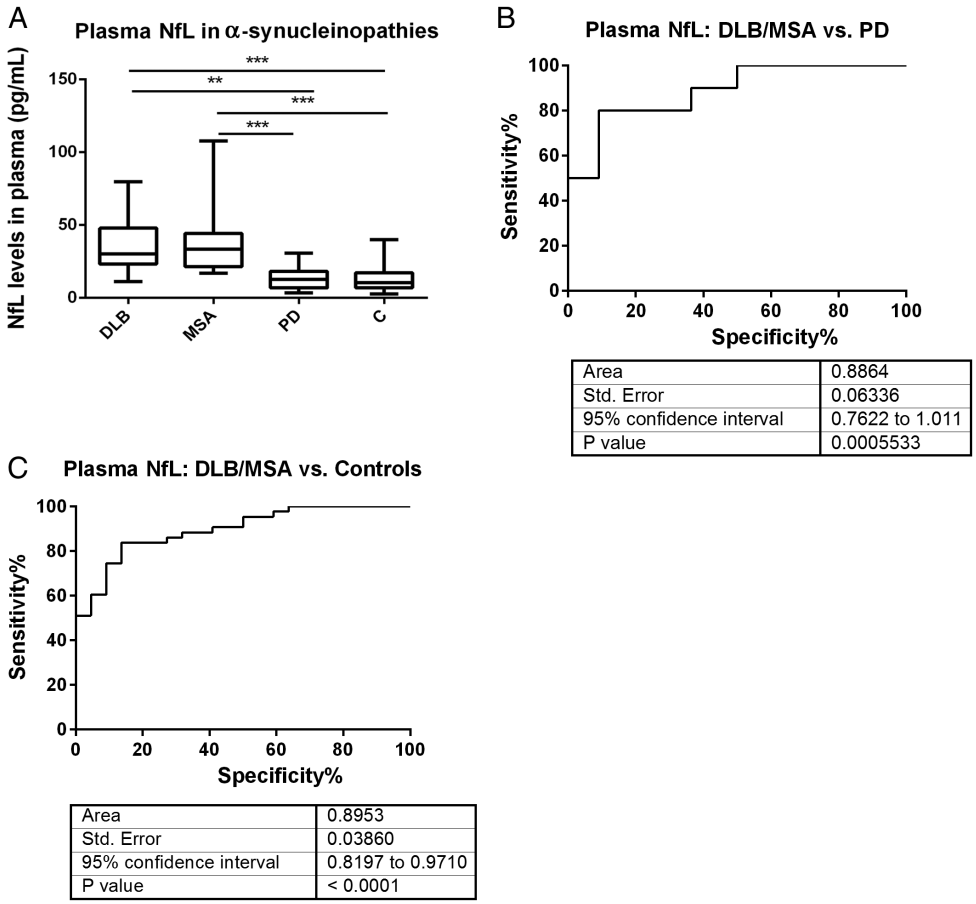

Area	0.8864
Std. Error	0.06336
95% confidence interval	0.7622 to 1.011
P value	0.0005533

Area	0.8953
Std. Error	0.03860
95% confidence interval	0.8197 to 0.9710
P value	< 0.0001

FIG. 1. Detection of NfL levels in plasma of α-synucleinopathies by a single molecule array–based NfL detection assay. Plasma NfL levels were determined in controls (n = 49) and patients with different types of α-synucleinopathies: DLB (n = 9), MSA (n = 13), and PD (n = 11). (**A**) Plasma NfL levels in patients with DLB and patients with MSA were significantly enhanced in comparison with patients with PD and controls. (**B**, **C**) Receiver operating characteristic curve analysis of plasma NfL levels from other α-synucleinopathies (MSA and DLB) in comparison with PD and controls revealed good diagnostic accuracy as indicated by area under the curve (AUC) values. AUC values (with 95% confidence intervals) for the discrimination of other α-synucleinopathies from patients with PD and controls were calculated. A *P* value <0.001 was considered as extremely significant (***), <0.01 was considered as very significant (**), and ≥0.05 was considered as not significant. C, controls; DLB, dementia with Lewy bodies; MSA, multiple system atrophy; NfL, neurofilament light chain; PD, Parkinson's disease.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Data

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Orthostatic Hypotension in Parkinson's Disease: Do Height and Weight Matter?

Every third person with Parkinson's disease (PD) may suffer from orthostatic hypotension (OH).[1] Besides classic OH (cOH), transient orthostatic blood pressure (BP) drops may occur within the first minute upon standing, qualifying for transient OH (tOH).[2] It is unclear whether morphometric factors, such as height and body mass index (BMI),[3] promote OH in people with PD.

For this reason, we analyzed a previously published cohort of 173 European patients with PD for differences in height and BMI across individuals with laboratory-confirmed cOH, tOH, or no OH.[2]

After comparing the morphometric and other clinicodemographic characteristics across patients with and without OH, we tested the association between BMI, height, and cOH or tOH, by calculating the area under the receiver operating characteristic (ROC) curve in males and females separately. The Youden index applied to the coordinates of the ROC curves determined the most accurate BMI and height cut-offs distinguishing patients with either cOH or tOH from those without. Whenever significant cut-offs were found, we compared the derived subgroups for differences in clinicodemographic features and autonomic function indices by means of univariate, binary logistic regression analysis and age-adjusted ANOVA for repeated measurements.

The clinicodemographic features of the study population are reported elsewhere.[2] In our cohort, cOH occurred in 19% (n = 32) of patients and tOH in 24% (n = 41).

BMI did not differ between patients with either cOH ($P = 0.270$) or tOH ($P = 0.798$) compared with those without OH (Fig. 1).

The ROC curve analysis excluded any differences in height among female patients with or without OH, but pinpointed a positive association between cOH and taller stature in male patients (Fig. 1). Male patients with cOH did not otherwise differ for any other clinicodemographic characteristic from those with tOH or no OH. The Youden index identified a height cut-off of ≥172.5 cm for predicting cOH in male patients with PD (Fig. 1). Both univariate and age-adjusted logistic regression analysis confirmed a negative association between cOH and shorter stature in males (odds ratio = 0.14 [95% confidence interval, 0.03–0.66]; $P = 0.013$), despite higher, yet not significant after Benjamini–Hochberg correction, frequencies of cardiovascular comorbidities and use of antihypertensive medications (Supporting Information Table S1).

At hemodynamic monitoring, shorter patients showed an average systolic BP increase after 3 minutes on standing, while patients ≥172.5 cm tall had a decrease ($P = 0.030$; Supporting Information Fig. S1). The remaining cardiovascular autonomic function indices did not differ across the height groups (Supporting Information Fig. S1).

Pilot studies in Asian PD populations suggested an association between lower BMI and cOH.[4-6] Here we did not observe any difference in BMI across male or female patients with PD with either cOH, tOH or no OH. This inconsistency possibly reflects ethnic and morphometric differences between European and Asian natives.

Elderly, otherwise healthy, shorter subjects show higher BP values compared with taller subjects, potentially reflecting underlying hydrostatic mechanisms.[7] The fact that cardiovascular autonomic function indices other than cOH were equally impaired in shorter and taller patients suggests that analogous, non-neurogenic mechanisms may prevent shorter individuals with PD from developing clinically relevant BP declines on standing.

Identifying individual OH risk factors may optimize screening measures for this frequently overlooked condition.

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Data Availability Statement

Due to the retrospective nature of the study, no ethic approval or written informed consent was due. We performed the study in accordance with the Declaration of Helsinki and the current European data protection regulation. The first and last author take responsibility for the integrity of the data and the accuracy of the data analysis. The authors have full access to all of the data, have the right to publish any and all data separate and apart from any sponsor, to obtain independent statistical analyses of the data. We agree to share any data not published within this article upon reasonable request from any qualified investigator.

Key Words: Parkinson's disease; orthostatic hypotension; body mass index; height

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