Subclinical Cardiac Microdamage, Motor Severity, and Cognition in Parkinson’s Disease

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ABSTRACT: Background: We assessed if cardiac blood markers are associated with motor and cognitive function in patients with Parkinson’s disease (PD).

Methods: High-sensitivity troponin I and N-terminal pro-B-type natriuretic peptide (NT-proBNP) were evaluated in 285 PD patients. Furthermore, N-terminal

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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.
Pathophysiological mechanisms underlying Parkinson’s disease (PD) involve energy metabolism, mitochondrial dysfunction, protein aggregation, and lysosomal malfunctioning. Similar mechanisms in cardiomyocytes are also involved in heart failure (HF) and can cause cardiac damage. Interestingly, epidemiological evidence revealed a link between PD and HF. Cardiovascular autonomic failure is frequent in untreated PD patients and progresses with disease severity. Recently, cardiovascular risk factors, such as diabetes and arterial hypertension, were also associated with PD, suggesting common hazardous processes for heart and brain in PD patients, but these association are still debated. Furthermore, genetic PD mouse and Drosophila models revealed impaired mitochondrial function and increased reactive oxygen species generation in cardiomyocytes, leading to heart failure. In the present study, we aimed to evaluate the potential association of subclinical blood-based cardiac biomarkers (i.e., high-sensitivity troponin I [hs-TnI] and N-terminal pro-B-type natriuretic peptide [NT-proBNP]) with motor and cognitive function in PD patients.

Methods

Study Design, Ethical Approval, and Patient Consent

The Biomarkers in Parkinson’s Disease study is a prospective observational single-center biobank at the University Medical Center Hamburg-Eppendorf. For the discovery and validation cohort, 57 and 228 patients with Parkinson’s disease, respectively, were recruited in the Department of Neurology at the University Medical Center Hamburg-Eppendorf from June 2017 to October 2017 and from October 2017 to April 2019, respectively. A detailed description is available in the Supporting Information.

Clinical Assessment

The clinical assessments are described in the Supporting Information.

Laboratory Analysis

The laboratory measurements were obtained from blood samples collected at baseline and processed as previously described. A detailed description is available in the Supporting Information.

Statistical Analysis

The statistical analyses are described in the Supporting Information.

Results

Patient Characteristics

In the pooled cohort, 285 PD patients were included, with an average age of 66.5 ± 9.3 years and a disease duration of 12.0 ± 7.0 years, and 64.2% were male (Table 1). The validation cohort of 228 PD patients had significantly lower high-sensitivity troponin I (hsTnI) levels, a higher estimated glomerular filtration rate (eGFR) and more dopamine agonist-treated patients compared with the discovery cohort of 57 PD patients (Table 1).

Cardiac Biomarkers in Healthy and PD Patients

N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels were above a clinical cutoff value of 125 ng/L in 49.9%, and high-sensitivity troponin I (hsTnI) levels were above a clinical cutoff of 27 ng/L in 1.4% of PD patients. Patients with NT-proBNP levels above the clinical cutoff were older, more likely to have prevalent hypertension, atrial fibrillation, prior myocardial infarction, prior stroke, or DBS, had higher low-density lipoprotein (LDL), triglyceride, creatinine, hsTnI, Unified Parkinson’s Disease Rating Scale (UPDRS) III, and Hoehn and Yahn (H&Y) stage and lower eGFR and Montreal Cognitive Assessment (MoCA) scores (Supporting Information Table S1). Mean NT-proBNP levels were 115 ng/L (IQR, 61–270 ng/L) in PD patients and thus significantly higher compared with age-, sex-, and vascular risk factor–matched controls (69 ng/L; IQR, 40–96 ng/L; P < 0.001;
Both, NT-proBNP and hsTnI were significantly correlated with age, but not with disease duration (Supporting Information Table S2). Cardiac biomarker levels did not differ between PD patients with and without dysautonomia (Supporting Information Table S3).

Cardiac Biomarkers and Motor Function

In the discovery, validation, and pooled cohorts, hsTnI levels were significantly associated with UPDRS III scores in fully adjusted linear regression analyses (Table 2 and Supporting Information Table S4). In addition to UPDRS III, hsTnI levels were also
TABLE 2. Association of cardiac biomarkers (hsTnI, NT-proBNP) with motor and cognitive function (UPDRS, Hoehn & Yahr, MoCA) in the pooled cohort of 285 PD patients

| Model | β coefficient (95% CI) | P | Odds ratio (95% CI) | P | β coefficient (95% CI) | P |
|-------|------------------------|---|---------------------|---|------------------------|---|
|       |                        |   |                      |   |                        |   |
| hsTnI |                        |   |                      |   |                        |   |
| 1     | 0.746 (0.458–1.033)    | < 0.001<sup>c</sup> | 1.263 (1.150–1.386) | < 0.001<sup>c</sup> | –0.173 (–0.300 to –0.079) | 0.003<sup>b</sup> |
| 2     | 0.521 (0.198–0.843)    | 0.002<sup>a</sup> | 1.224 (1.108–1.352) | < 0.001<sup>c</sup> | –0.066 (–0.183 to 0.052) | 0.27 |
| 3     | 0.585 (0.254–0.917)    | 0.001<sup>b</sup> | 1.213 (1.094–1.344) | < 0.001<sup>c</sup> | –0.047 (–0.160 to 0.066) | 0.42 |
| NT-proBNP |                        |   |                      |   |                        |   |
| 1     | 0.009 (0.005–0.013)    | < 0.001<sup>c</sup> | 1.002 (1.001–1.004) | < 0.001<sup>c</sup> | –0.004 (–0.005 to –0.002) | < 0.001<sup>c</sup> |
| 2     | 0.005 (0.000–0.010)    | 0.037<sup>a</sup> | 1.002 (1.000–1.003) | 0.007<sup>b</sup> | –0.001 (–0.003 to 0.001) | 0.20 |
| 3     | 0.007 (0.002–0.012)    | 0.007<sup>a</sup> | 1.001 (1.000–1.003) | 0.019<sup>b</sup> | –0.001 (–0.003 to 0.001) | 0.14 |

Linear regression analysis with beta coefficients (95% CI) and logistic regression analysis with odds ratio (95% CI): model 1; unadjusted; model 2, adjusted for age, sex, and creatinine; model 3, also adjusted for disease duration, dysautonomia, hypertension, diabetes, hypercholesterolemia, prior myocardial infarction, prior stroke, atrial fibrillation, and body mass index.

<sup>a</sup>P < 0.05.
<sup>b</sup>P < 0.01.
<sup>c</sup>P < 0.001.
n = 285.

significantly higher in patients with advanced H&Y stage (>2) compared with lower (<2) H&Y stage (discovery cohort, 3.07 vs 7.32 ng/L; P = 2 × 10<sup>−4</sup>; validation cohort, 3.02 vs 5.97 ng/L; P = 6 × 10<sup>−6</sup>; pooled cohort, 3.03 vs 6.26 ng/L; P = 1 × 10<sup>−5</sup>). In all 3 cohorts, this difference remained significant after multiple adjustments in logistic regression analysis (Table 2 and Supporting Information Table S5). In the discovery, validation and pooled cohorts, NT-proBNP was also associated with UPDRS III in unadjusted models, but remained significant only in the pooled cohort after full adjustment (Table 2 and Supporting Information Table S4). Similarly, patients with advanced H&Y stage (>2) revealed significantly higher NT-proBNP levels compared with lower (<2) H&Y stage (discovery cohort, 148 vs 424 ng/L; P = 0.002; validation cohort, 158 vs 339 ng/L; P = 2 × 10<sup>−4</sup>; pooled cohort, 156 vs 358 ng/L; P = 2 × 10<sup>−6</sup>). In logistic regression analysis, this difference was significant in all 3 cohorts using unadjusted models, but remained significant only in the validation and pooled cohorts after multiple adjustments (Table 2 and Supporting Information Table S5).

Cardiac Biomarkers and Motor and Cognitive Decline

One hundred one patients of the pooled PD cohort were readmitted to our clinic after 1 year (338 ± 107 days). These patients were stratified into 2 groups according to their median hsTnI level at baseline (ie, ≤2.6 and > 2.6 ng/L). Patients with hsTnI levels ≤2.6 ng/L compared with patients with hsTnI levels >2.6 ng/L were younger, had less frequent hypertension and had a lower body mass index and creatinine (Supporting Information Table S7). Disease duration and UPDRS III at baseline did not differ between groups. After 1 year, patients with baseline hsTnI levels ≤2.6 ng/L had significantly lower UPDRS III scores compared with patients with hsTnI levels >2.6 ng/L (≤2.6 ng/L, 20.0 ± 4.0; >2.6 ng/L, 27.2 ± 10.8; P < 0.05; Supporting Information Fig. S1A). Similar results were observed comparing patients with low and high NT-proBNP levels (ie, ≤95 vs >95 ng/lng/L). High NT-proBNP levels in PD patients at baseline had worse UPDRS III scores after 1 year despite similar UPDRS III scores at baseline and time to follow up (Supporting Information Fig. S1B). After adjustment for age and disease duration, the association of hsTnI and NT-proBNP with UPDRS III scores at follow-up remained significant (P = 0.01 and P = 0.02, respectively). Patients with NT-proBNP levels ≤95 ng/lng/L were significantly younger, were more likely male, and had higher eGFRs and MoCA score but lower hsTnI levels (Supporting Information Table S8). Concerning...
cognitive function, we did not observe a change in MoCA score between patients with low and high hsTnI or NT-proBNP levels after 1 year (Supporting Information Fig. S1).

**Discussion**

Our findings reveal that (1) NT-proBNP is increased in PD patients, (2) NT-proBNP and hsTnI are associated with motor function, and (3) increased hsTnI at baseline is associated with motor decline after 1 year.

Increased NT-proBNP levels indicate subclinical cardiomyopathy or cardiac stress. Although autonomic denervation might be a straightforward explanation, we did not observe an association of cardiac biomarkers with autonomic dysfunction. Recently, cardiovascular risk factors were identified as risk markers for PD incidence and for faster disease progression. In our study, the association between motor function and cardiac biomarkers was consistent in the discovery and validation cohorts after adjusting for cardiovascular risk factors, suggesting that these factors do not solely explain this association. We rather suggest that nigrostriatal degeneration and subclinical cardiomyopathy progress parallel to each other and are caused by common pathophysiological and cellular mechanisms.

In line with this hypothesis, previous findings have suggested a number of pathophysiological mechanisms that might underlie both entities. Neuropathological studies revealed that α-synuclein aggregates were as common in heart as in central and peripheral neurons of PD patients. Both cell types express a similar repertoire of ion channels and receptors, have a high fluctuating energy demand and are therefore especially prone to damage by mitochondrial dysfunction and oxidative stress. In addition to neuropathological studies, genetic findings link PD and cardiac dysfunction. Parkinson susceptibility genes, like PARK2, PARK7, and PARK8, are involved in mitochondrial function and reduction of oxidative stress. Interestingly, PARK2-, PARK7-, and PARK8-deficient mice develop cardiac hypertrophy accompanied by increased oxidative stress and mitochondrial dysfunction. Our epidemiological data underline these findings, providing evidence that motor impairment and progression correlate with markers of cardiac injury and cardiomyopathy independent of traditional vascular risk factors.

Finally, cardiac biomarkers have been associated with cognitive function and dementia independent of traditional cardiovascular risk factors in population-based cohorts. Cross-sectional studies suggested that NT-proBNP was associated with brain volume independent of cardiac output. In prospective studies, higher NT-proBNP levels were associated with an increased risk of dementia and cognitive decline. In our study, hsTnI and NT-proBNP were only associated with cognitive function in unadjusted models and therefore did not reveal a robust link between cardiac biomarkers and cognition in PD.

A limitation of our study is the case-control and cross-sectional design, which does not allow drawing causal relationships. Furthermore, the study included hospital-based prevalent PD cases with advanced disease at baseline and treatment with anti-PD medication for years. Therefore, it is not possible to differentiate effects of PD progression and treatment. Although we present prospective data on a subset of patients, the size of this subcohort is very small and does not allow controlling for covariates. Furthermore, follow-up data were assessed in patients, who were readmitted to our outpatient clinic and thereby underlined a selection bias. Cardiovascular risk was evaluated using medical records and not according to current cardiological investigations (ie, echocardiography, electrocardiogram, coronary angiography).

In our study, subclinical serum markers of cardiac injury were associated with Parkinson’s disease itself (NT-proBNP) and current and possibly future motor function (NT-proBNP and hsTnI) independent of traditional vascular risk factors. Our data emphasize the importance of evaluating the heart-brain axis in PD pathology.

**References**

1. Giannoccaro MP, La Morgia C, Rizzo G, Carelli V. Mitochondrial DNA and primary mitochondrial dysfunction in Parkinson’s disease. Mov Disord 2017;32(3):346–363.

2. Lang AE, Espay AJ. Disease modification in Parkinson’s disease: current approaches, challenges, and future considerations. Mov Disord 2018;33(5):660–677.

3. Murphy E, Ardehali H, Balaban RS, et al. Mitochondrial function, biology, and role in disease: a scientific statement from the American Heart Association. Circ Res 2016;118(12):1960–1991.

4. Piqueras-Flores J, Lopez-Garcia A, Moreno-Reig A, et al. Structural and functional alterations of the heart in Parkinson’s disease. Neurou Res 2018;40(1):53–61.

5. Zesiewicz TA, Strom JA, Borenstein AR, et al. Heart failure in Parkinson’s disease: analysis of the United States medicare current beneficiary survey. Parkinsonism Relat Disord 2004;10(7):417–420.

6. Watanabe M, Takada T, Nakamagoe K, Tamaoka A. Sequential imaging analysis using MBG scintigraphy revealed progressive degeneration of cardiac sympathetic nerve in Parkinson’s disease. Eur J Neurol 2011;18(7):1010–1013.

7. Kummer BR, Diaz I, Wu X, et al. Associations between cerebrovascular risk factors and Parkinson disease. Ann Neurol 2019;86(4):572–581.

8. Malek N, Lawton MA, Swallow DM, et al. Vascular disease and vascular risk factors in relation to motor features and cognition in early Parkinson’s disease. Mov Disord 2016;31(10):1518–1526.

9. Ascherio A, Schwarzschild MA. The epidemiology of Parkinson’s disease: risk factors and prevention. Lancet Neurol 2016;15(12):1257–1272.
A Gain-of-Function Mutation in KCNMA1 Causes Dystonia Spells Controlled With Stimulant Therapy

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ABSTRACT: Background: The mutations of KCNMA1 BK-type K+ channel have been identified in patients with various movement disorders. The underlying pathophysiologic and corresponding therapeutics are lacking. 

Objectives: To report our clinical and biophysical characterizations of a novel de novo KCNMA1 variant, as well as an effective therapy for the patient’s dystonia-atonia spells.

Methods: Combination of phenotypic characterization, therapy, and biophysical characterization of the patient and her mutation.

Results: The patient had >100 dystonia-atonia spells per day with mild cerebellar atrophy. She also had autism spectrum disorder, intellectual disability, and attention deficit hyperactivity disorder. Whole-exome sequencing identified a heterozygous de novo BK N536H mutation. Our biophysical characterization demonstrates that N536H is a gain-of-function mutation with markedly enhanced voltage-dependent activation.

Supporting Data

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

1. Billia F, Hauk L, Grothe D, et al. Parkinson-susceptibility gene DJ-1/PARK7 protects the murine heart from oxidative damage in vivo. Proc Natl Acad Sci U S A 2013;110(15):6085-6090.
2. Billia F, Hauk L, Konceny F, Rao V, Shen J, Mak TW. PTEN-inducible kinase 1 (PINK1)/Park6 is indispensable for normal heart function. Proc Natl Acad Sci U S A 2011;108(23):9572-9577.
3. Bhandari P, Song M, Chen Y, Barelle Y, Dorn GW 2nd. Mitochondrial contagion induced by Parkin deficiency in Drosophila hearts and its containment by suppressing mitofusin. Circ Res 2014;114(2):257-265.
4. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)/Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37(27):2129-2200.
5. Mollenhauer B, Zimmermann J, Sixel-Doring F, et al. Baseline predictors for progression 4 years after Parkinson’s disease diagnosis in the De Novo Parkinson Cohort (DeNoPa). Mov Disord 2019;34(1):67-77.
6. Gelpi E, Navarro-Otano J, Tolosa E, et al. Multiple organ involvement by alpha-synuclein pathology in Lewy body disorders. Mov Disord 2014;29(8):1010-1018.
7. Terman A, Kurz T, Navratil M, Arriaga EA, Brunk UT. Mitochondrial turnover and aging of long-lived postmitotic cells: the mitochondrial-lysosomal axis theory of aging. Antioxid Redox Signal 2010;12(4):503-535.
8. Bertens AS, Sabayan B, de Craen AJM, Van der Mast RC, Gussekloo J. High sensitivity cardiac troponin T and cognitive function in the oldest old: the Leiden 85-Plus Study. J Alzheimers Dis 2017;60(1):235-242.
9. Mirza SS, de Brujin RF, Koudstaal PJ, et al. The N-terminal pro B-type natriuretic peptide, and risk of dementia and cognitive decline: a 10-year follow-up study in the general population. J Neurol Neurosurg Psychiatry 2016;87(4):356-362.
10. Schneider AL, Rawlings AM, Sharrett AR, et al. High-sensitivity cardiac troponin T and cognitive function and dementia risk: the atherosclerosis risk in communities study. Eur Heart J 2014;35(27):1817-1824.
11. Tynkkynen J, Hernesniemi JA, Laatikainen T, et al. High-sensitivity cardiac troponin I and NT-proBNP as predictors of incident dementia and Alzheimer’s disease: the FINRISK Study. J Neurol 2017;264(3):503-511.
12. Sabayan B, van Buchem MA, de Craen AJ, et al. N-terminal pro-brain natriuretic peptide and abnormal brain aging: the AGES-Reykjavik Study. Neurology 2015;85(9):813-820.
13. MGJ, Henry RMA, Brunner-La Rocca HP, et al. Cross-sectional associations between cardiac biomarkers, cognitive performance, and structural brain changes are modified by age. Arterioscler Thromb Vasc Biol 2018;38(8):1948-1958.
14. Kerola T, Nieminen T, Hartikainen S, Sulkava R, Vuollehto O, Kettunen R. B-type natriuretic peptide as a predictor of declining cognitive function and dementia—a cohort study of an elderly general population with a 5-year follow-up. Ann Med 2010;42(3):207-215.
15. Wijmans LW, Sabayan B, van Vliet P, et al. N-terminal pro-brain natriuretic peptide and cognitive decline in older adults at high cardiovascular risk. Ann Neurol 2014;76(2):213-222.