Serum FGF-21, GDF-15, and blood mtDNA copy number are not biomarkers of Parkinson disease

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Abstract

Background

Strong evidence of mitochondrial dysfunction exists for both familial and sporadic Parkinson disease (PD). A simple test, reliably identifying mitochondrial dysfunction, could be important for future stratified medicine trials in PD. We previously undertook a comparison of serum biomarkers in classic mitochondrial diseases and established that serum growth differentiation factor 15 (GDF-15) outperforms fibroblast growth factor 21 (FGF-21) when distinguishing patients with mitochondrial diseases from healthy controls. This study aimed to systematically assess serum FGF-21 and GDF-15, together with mitochondrial DNA (mtDNA) copy number levels in peripheral blood cells from patients with PD and healthy controls, to determine whether these measures could act as a biomarker of PD.

Methods

One hundred twenty-one patients with PD and 103 age-matched healthy controls were recruited from a single center. Serum FGF-21 and GDF-15, along with blood mtDNA copy number, were quantified using established assays.

Results

There were no meaningful differences identified for any of the measures when comparing patients with PD with healthy controls. This highlights a lack of diagnostic sensitivity that is incompatible with these measures being used as biomarkers for PD.

Conclusion

In this study, serum FGF-21, serum GDF-15, and blood mtDNA levels were similar in patients with PD and healthy controls and therefore unlikely to be satisfactory indicators of mitochondrial dysfunction in patients with PD.

Classification of evidence

This study provides Class III evidence that serum FGF-21, serum GDF-15, and blood mtDNA copy number levels do not distinguish patients with PD from healthy controls. There was no diagnostic uncertainty between patients with PD and healthy controls.

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A mitochondrial biomarker in sporadic PD would be of considerable benefit to provide evidence of target engagement during clinical trials.

Parkinson disease (PD) continues to be relentlessly progressive. Mitochondrial dysfunction is a key mechanism in the pathogenesis of both sporadic and familial forms of PD.^{1,2} Failure of all previous clinical trials assessing mitochondrial rescue compounds, such as MitoQ, for their neuroprotective effect may reflect our current inability to identify those patients with PD with particularly marked mitochondrial dysfunction and stratify them accordingly. A mitochondrial biomarker in sporadic PD would be of considerable benefit to provide evidence of target engagement during clinical trials.

Recent studies have identified serum biomarkers associated with classic mitochondrial diseases, namely fibroblast growth factor 21 (FGF-21) and growth differentiation factor 15 (GDF-15).^{3–5} FGF-21 is a regulator of glucose and fatty acid metabolism in the body. FGF-21 is present in the brain, including the substantia nigra, and is expressed by glial cells in culture.⁶ In dopaminergic neurons, FGF-21 increases the levels of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and enhances mitochondrial respiratory function.⁶ PGC-1α is a mitochondrial master regulator that is downregulated in PD.⁷ GDF-15 is predominantly expressed in the liver.⁸ In the brain, its most prominent site of synthesis is the choroid plexus, which secretes GDF-15 into the CSF from where the molecule can penetrate through the ependymal layer into the parenchyma.⁹ Evidence of its neuroprotective effect in different toxin-induced rodent models of PD is conflicting.^{10,11} Serum levels of GDF-15 were found to be increased in Chinese patients with PD compared with controls.¹² In contrast, GDF-15 levels in the CSF were similar in German nondemented PD patients and controls, but increased in patients with PD and dementia and patients with Lewy body dementia. GDF-15 levels were also found to correlate with age at onset of parkinsonism and age at onset of dementia, as well as with the neurodegenerative markers t-Tau and p-Tau. However, GDF-15 levels did not correlate with disease duration.¹³

Changes in the mitochondrial DNA (mtDNA) copy number typically reflect altered mitochondrial biogenesis. Circulating cell-free mtDNA is reduced in the CSF of patients with early-stage PD compared with controls.¹⁴ A reduction of the mtDNA copy number in peripheral blood cells (PBCs) has also been reported in two different PD patient populations.^{14,15} In Chinese patients with PD, a lower

mtDNA copy number was more frequently detected in an older age onset group.¹⁵

As mitochondrial dysfunction is intimately associated with PD pathogenesis and progression, these simple indicators of impaired mitochondrial function in peripheral blood may provide diagnostic utility for identifying patients with PD and monitoring disease progression. Therefore, this study investigated serum FGF-21, serum GDF-15, and mtDNA copy number in PBCs as potential disease indicators in a cohort of patients with clinically established PD.

Methods

Primary research question and classification of evidence

Can serum FGF-21, serum GDF-15, or relative mtDNA content of PBCs be useful biomarkers for PD? This is a diagnostic case-control study providing Class III evidence with no diagnostic uncertainty between healthy controls and patients with PD.

Subjects

Prospective samples were collected between 2011 and 2013 from a convenience cohort at the Royal Hallamshire Hospital, Sheffield, UK, and Doncaster Royal Infirmary, Doncaster, UK. The diagnosis of PD was based on the Queen Square Brain Bank criteria for the diagnosis of PD. Patients with PD were recruited if they satisfied the recruitment criteria, along with an age- and sex-matched healthy control group consisting of independent volunteers or spouses of patients.

Standard protocol approvals, registrations, and patient consents

Written informed consent was obtained from all subjects in the study in accordance with institutional ethics approval (STH16350). A summary of the recruitment, cohort, exclusion, and analysis is provided in the Standards for Reporting of Diagnostic Accuracy Studies (STARD) diagram (figure 1).

Procedures

Blood was collected into BD Vacutainer® SSTTM and Whole Blood K₂EDTA tubes (Becton, Dickinson and Company, NJ). Serum was stored in aliquots at –80°C. Total genomic DNA was extracted from whole blood using the Nucleon BACC Genomic DNA extraction kit (GE Healthcare Life Sciences, Buckinghamshire, United Kingdom).

Operators (R.L.D. and S.L.W.) were blinded to sample groupings when performing assays. Serum FGF-21 levels were measured in duplicate with the Quantikine Human FGF-21 ELISA kit (R&D Systems, MN), according to the manufacturer's protocol. Serum GDF-15 levels were

Figure 1 Standards for Reporting of Diagnostic Accuracy Studies (STARD)

Details of cohort recruitment, subject and sample exclusion, and overall sample data analysis for this study.

measured in triplicate using the Human GDF-15 ELISA kit (BioVendor, Czech Republic), according to the manufacturer's protocol.

Relative mtDNA content was determined by comparing mitochondrial *MT-ND1* with the single copy nuclear-encoded *B2M* using SYBR Green (Applied Biosystems, CA) quantitative real-time PCR. Patients with PD and healthy control samples were analyzed in order of recruitment, which resulted in a random assignment to each quantitative PCR run, thus reducing the assay bias. Relative mtDNA content was calculated using the equation: Relative mtDNA content = $2 \times 2^{\Delta C_t}$.¹⁶

Statistical analysis

Statistical analyses were performed using SPSS version 24 (IBM, NY), with $p < 0.05$ considered statistically significant. The 95th percentile of healthy control measurements was taken as a threshold cutoff for diagnostic sensitivity. Diagnostic sensitivity was determined using Clinical Research Calculator 1 on the Vassar Stats website (vassarstats.net/). The probability of a given assay indicating disease if the levels

were raised was determined from the area under a receiver operating characteristics curve.

Data availability

Raw data are available on request.

Results

Cohort parameters

The cohort comprised 103 healthy controls and 121 patients with PD (figure 1 and table). The PD group could be subcategorized into 37 patients with early-onset PD (EOPD) and 84 patients with late-onset PD (LOPD). The average age ($\pm$ SEM; range) for the healthy control group (61.4 ± 1.2 years; 27–83 years) and the PD group (63.6 ± 0.9 years; 38–83 years) were not statistically different ($p = 0.252$). The healthy control group had a sex balance of 54% female to 46% male, compared with 38% female and 62% male in the PD group, consistent with the reported 1.5 times higher incidence rate in males.¹⁷ The average age at disease onset ($\pm$ SEM; range) for patients with EOPD was 42.4 years (± 1.3 ;

Table Summary of study cohort and measured biomarker data

	Healthy control	Parkinson disease (PD)	Early-onset PD	Idiopathic PD
n	103	121	37	84
Mean age ($\pm$SEM; min-max)	61.4 ($\pm$ 1.2; 27-83)	63.6 ($\pm$ 0.9; 38-83)	52.4 ($\pm$ 1.2; 38-66)	68.5 ($\pm$ 0.8; 52-83)
Mean age at onset ($\pm$SEM; min-max)	—	56.6 ($\pm$ 1.1; 16-81)	42.4 ($\pm$ 1.3; 16-50)	62.9 ($\pm$ 10.8; 50-81)
Sex (%F: %M)	54%: 46%	38%: 62%	32%: 68%	40%: 60%
Mean FGF-21 (pg/mL) ($\pm$SEM)	269.7 ($\pm$ 32.1)	217.9 ($\pm$ 19.8)	251.1 ($\pm$ 51.5)	203.1 ($\pm$ 17.2)
Median FGF-21 (pg/mL) (IQR)	187 (213)	165 (168.5)	170 (220.5)	165 (154)
Mean GDF-15 (pg/mL) ($\pm$SEM)	2542.7 ($\pm$ 205.8)	2603.1 ($\pm$ 192.7)	2517.9 ($\pm$ 567.7)	2640.5 ($\pm$ 125.3)
Median GDF-15 (pg/mL) (IQR)	1868 (1558)	2162 (1205)	1741 (1227.5)	2281 (1263.3)
Mean relative mtDNA content ($\pm$SEM)	88.61 ($\pm$ 11.8)	96.6 ($\pm$ 13.3)	69.24 ($\pm$ 17.3)	108.47 ($\pm$ 17.5)

Abbreviations: IQR = interquartile range; PD = Parkinson disease; SEM = standard error of the mean.

16–50 years) and for patients with LOPD was 62.9 years ($\pm$ 10.8; 50–81 years).

Biomarkers

The median levels of serum FGF-21 were similar for the healthy control group (187 pg/mL, interquartile range [IQR] = 221.0 pg/mL) and the combined PD patient cohort (165 pg/mL, IQR = 168.5 pg/mL; $p = 0.45$). Consistently, a difference was not identified for serum FGF-21 concentrations ($p = 0.75$) when comparing healthy control, EOPD, and LOPD groups separately by Kruskal-Wallis testing (figure 2A).

The median levels of serum GDF-15 (figure 2A) for the healthy control (1868 pg/mL, IQR = 1558 pg/mL) and the entire PD cohort (2162 pg/mL, IQR = 1205 pg/mL) groups were not

statistically different either ($p = 0.07$). However, inference of a difference was identified ($p = 0.02$) when comparing GDF-15 serum levels in healthy control, EOPD, and LOPD groups by Kruskal-Wallis testing. Mann-Whitney U testing showed differences in GDF-15 levels between the LOPD (2281 pg/mL, IQR = 1263.25 pg/mL) group compared with both the healthy control (1868 pg/mL, IQR = 221.0 pg/mL, $p = 0.0049$) and EOPD (1741 pg/mL, IQR = 1227.5 pg/mL, $p = 0.001$) groups (figure 2A). However, because of the extensive overlap of GDF-15 concentrations between the healthy control and PD groups, this statistical significance is unlikely to indicate biological or clinical significance.

The median relative mtDNA content in peripheral blood leukocytes (figure 2B) for healthy controls was 52.7

Figure 2 Group comparisons of serum biomarkers and peripheral blood mtDNA content

(A) Comparison of FGF-21 and GDF-15 serum biomarker concentrations. Statistical differences were apparent between the patients with late-onset PD compared with early-onset PD and the healthy control group. Box and whiskers show the maximum to minimum, quartiles, and median. Mean is also shown as "+". (B) Comparison of relative mtDNA content from peripheral blood leukocytes. No differences between groups were apparent. Lines denote quartiles and median. mtDNA = mitochondrial DNA.

(range = 759, IQR = 55.95) and 44.3 for patients with PD (range = 807, IQR = 70.91). However, there was no difference between healthy control and PD patient relative mtDNA content ($p = 0.348$ by Mann-Whitney U analysis). When comparing the healthy control, EOPD, and LOPD groups separately (figure 2B), there was also no difference apparent ($p = 0.386$ by Kruskal-Wallis analysis).

Numerous correlations between the measured parameters were identified in each of the cohort groups using non-parametric Spearman correlation comparisons (figure 3, A–E). For the healthy control group, a strong correlation was apparent between age and GDF-15 (figure 3A: $r_s = 0.659$, $p = 3.6 \times 10^{-14}$), and a weak correlation was evident between FGF-21 and GDF-15 (figure 3B: $r_s = 0.289$, $p = 0.003$). For the PD group, multiple correlations were identified; a strong correlation was again apparent between age and GDF-15 (figure 3C: $r_s = 0.585$, $p = 1.89 \times 10^{-12}$) as in the healthy control group, a moderate correlation between age at disease onset and GDF-15 (figure 3D: $r_s = 0.444$, $p = 4.23 \times 10^{-7}$), and weak correlations between disease duration and GDF-15 (figure 2F: $r_s = 0.240$, $p = 8.67 \times 10^{-3}$) and age at disease onset and relative mtDNA content (figure 2G: $r_s = 0.220$, $p = 0.0161$). Subsequent to linear regression analysis of correlative combinations, only age and FGF-21 levels remained associated with

GDF-15 ($p = 1.51 \times 10^{-7}$ and $p = 0.02$, respectively) in the healthy control group. Whereas, none of the correlations identified for the PD group remained after this analysis.

Diagnostic indications

Using the 95th percentile of the healthy control group serum biomarker concentrations (FGF-21 = 812 pg/mL, GDF-15 = 5854 pg/mL) and relative mtDNA content (339.8) as a threshold cutoff, both FGF-21 and GDF-15 provided diagnostic sensitivity of 1.65% (95% confidence intervals, FGF-21 = 0.3–6.5%, GDF-15 = 0.3–6.4%), and relative mtDNA content provided a diagnostic sensitivity of 8.4% (95% confidence interval = 4.3–15.3%). Receiver operating characteristic (ROC) curve analysis, using the area under the curve as a probability for correctly identifying a patient when biomarker levels are raised, gave areas of 53%, 57%, and 46.7% for FGF-21, GDF-15, and relative mtDNA content in PBCs respectively, which are only slightly better than chance. Consistently, none of the biomarkers tested showed an association with disease following multivariate logistic regression analysis (FGF-21, $p = 0.229$; GDF-15, $p = 0.791$; relative mtDNA content, $p = 0.687$).

Despite the observed differences outlined above, the overlap of biomarker concentrations (in particular GDF-15) between

Figure 3 Nonparametric correlations of measured parameters

Nonparametric Spearman rank-order correlations showed strong association between (A) GDF-15 and age in both patients with PD (red dots) and healthy controls (blue dots). Weak and moderate correlations were also apparent between (B) GDF-15 and FGF-21 in healthy controls, (C) GDF-15 and age at disease onset in patients with PD, (D) GDF-15 and disease duration in patients with PD, and (E) relative mtDNA content and age at onset in patients with PD. Subsequent to linear regression analysis of correlative combinations, only age and FGF-21 levels remained associated with GDF-15 ($p = 1.51 \times 10^{-7}$ and $p = 0.02$, respectively) in the healthy control group. mtDNA = mitochondrial DNA.

Our assessment of serum markers of mitochondrial dysfunction and blood mitochondrial DNA content as indicators of clinically established PD failed to show clinical or diagnostic utility.

healthy controls and patients with PD makes these tests indistinguishable markers for PD and would therefore be unsuitable for indicating disease, disease severity, or as a therapeutic end point.

Discussion

Our assessment of serum markers of mitochondrial dysfunction and blood mtDNA content as indicators of clinically established PD failed to show clinical or diagnostic utility. A suitable biomarker would fulfill the basic criteria of (1) sensitivity and specificity for preclinical or prodromal PD, (2) early emergence in the disease course, (3) ease and accuracy of measurement, and (4) indication of longitudinal changes in disease severity.¹⁸

The only other report on these serum markers was undertaken in a Chinese PD cohort and only investigated GDF-15.¹² This study identified a difference in GDF-15 levels between patients with idiopathic PD and healthy controls, with a diagnostic sensitivity of 71.2%, specificity of 82.5%, and an area under the receiver operating characteristic curve of 86%.¹² This is in stark contrast to our findings, showing that GDF-15 provides no meaningful diagnostic indication. The index study also identified differences in GDF-15 concentrations between sexes, with a higher diagnostic sensitivity for men. This is in contrast to our study where no difference was identified for either marker between patients, healthy controls, or disease controls, nor for sexes. The reason for this is not evident, as despite the clear differences in the concentrations measured by the different kits used for all marker measurements, the cohort differences should be relative for different types of assay. The previous study had similar patient (n = 104) and healthy control (n = 88) cohort sizes. Further confirmatory studies to determine whether GDF-15 may be a diagnostic marker in Chinese patients with PD are needed.

Strict regulation of the mtDNA copy number is essential for effective production of ATP through oxidative phosphorylation. Deletions and mutations of mtDNA lead to mitochondrial dysfunction, which is hypothesized to play a role in aging and neurodegeneration in PD.^{19,20} mtDNA deletions

may cause an increase in mtDNA copy number as a compensatory mechanism.²¹ The lack of any difference in mtDNA copy number in PBCs from patients with PD compared with healthy controls in this study is also in contrast to a previous report on British patients with PD and healthy controls.¹⁴ The discrepant results highlight the importance of replication studies. Quantification of circulating cell-free mtDNA may be a more promising diagnostic and prognostic marker in PD.²²

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Disclosure

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Name	Location	Contribution
Ryan L. Davis, PhD	University of Sydney and Royal North Shore Hospital, Sydney, Australia	Research project organization and execution; statistical analysis design, execution, review, and critique; and manuscript first draft preparation, review, and critique
Siew L. Wong, MD	University of Sheffield, Sheffield, United Kingdom	Research project organization and execution and manuscript review and critique
Phillippa J. Carling, PhD	University of Sheffield, Sheffield, United Kingdom	Research project organization and

Continued

Appendix (continued)

Name	Location	Contribution
		execution and manuscript review and critique
Thomas Payne, MD	University of Sheffield, Sheffield, United Kingdom	Research project organization and manuscript review and critique
Carolyn M. Sue MBBS, PhD	University of Sydney and Royal North Shore Hospital, Sydney, Australia	Research project conception and organization; statistical analysis review and critique; and manuscript review and critique
Oliver Bandmann, MD, PhD	University of Sheffield, Sheffield, United Kingdom	Research project conception, organization, and execution; statistical analysis design, execution, review, and critique; and manuscript first draft preparation, review, and critique

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