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BRIEF COMMUNICATION

Plasma neurofilament light chain levels are associated with depressive and anxiety symptoms in Parkinson's disease

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Abstract
The present study aimed to explore the association of plasma neurofilament light chain (NfL) levels with depression and anxiety in Parkinson's disease (PD). This prospective study enrolled 116 patients with PD and 38 healthy controls, and found plasma NfL levels were higher in patients with depression or anxiety than in those without these symptoms. Binary logistic regression identified NfL concentration as an independent predictor of depression and anxiety in PD. In conclusion, elevated plasma NfL may be associated with severity of depression and anxiety in PD patients and may serve as a diagnostic biomarker of PD with moderate to severe depression or anxiety.

Keywords Parkinson's disease · NfL · Depression · Anxiety · HAMD-17 · HAMA

Introduction

Depression and anxiety are frequent non-motor symptoms of Parkinson's disease (PD) that are associated with PD progression and severity. Plasma levels of neurofilament light chain (NfL) are a marker of neuro-axonal injury and have been linked to neurodegenerative diseases [1], specifically showing promising associations with cognitive impairment in Alzheimer's disease [2]. Recently, these levels have shown promising for distinguishing PD from atypical parkinsonian disorders, and there was a study that demonstrated that plasma NfL levels correlated with disease severity and progression in terms of both motor and cognitive functions in PD [3]. Thus, we wished to examine whether plasma NfL levels may also be linked to non-motor symptoms in PD.

Subjects and methods

From January 2017 to November 2020, we involved 116 PD patients and 38 healthy controls. Patients were included if they had been diagnosed with PD according to International Parkinson and Movement Disorder Society criteria in 2015 [4]. We excluded patients if they were (1) had definitively diagnosed psychiatric disorders; (2) currently receiving antidepressants or intracranial surgical treatments; and (3) had debilitating conditions that could impede full participation in the study. Health controls were recruited. The study was approved by the ethics committee of Kunming Medical University, and written informed consent was obtained from each participant.

Patients were categorized into four groups depending on severity of depression or anxiety, as measured using the 17-item Hamilton Rating Scale for Depression (HAMD-17) and Hamilton Rating Scale for Anxiety (HAMA). HAMD scores of >24 were defined as severe depression (PD-SD); 18 to 24, moderate depression (PD-MOD); 8 to 17, mild depression (PD-MID); and ≤ 7, no depression (PD-ND) [5]. HAMA scores of ≥ 24 were defined as severe anxiety (PD-SA); 15 to 23, moderate anxiety (PD-MOA); 8 to 14,

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mild anxiety (PD-MIA); and ≤ 7, no anxiety (PD-NA) [6]. Clinical data were collected. Detailed information on scales assessment and NfL testing is shown in Supplementary Appendix 1 (Online Resource 1).

Statistical analyses

Statistical analyses were conducted in SPSS 25.0. Differences associated with $p < 0.05$ were considered statistically significant. Numerical data were summarized as mean ± standard deviation and categorical data was presented as percentages using χ^2 test. Pearson correlation analyses were used to assess the correlation between variables. Using the PD combined with moderate to severe depression or anxiety as the end point, we performed binary logistic regression analyses to assess the relationship between plasma NfL levels and depressive or anxiety symptom. Diagnostic accuracy of plasma NfL levels was examined with the use of receiver operating characteristic curve (ROC) analyses.

Results

Demographical and clinical characteristics of the healthy controls and PD patients stratified by severity of depression symptoms are summarized in Table 1. Demographical and clinical characteristics of the healthy controls and PD patients stratified by severity of anxiety symptoms are summarized in Supplementary Table 1 (Online Resource 2). PD-SD and PD-MOD showed significantly higher Hoehn-Yahr stage (H&Y stages) than patients with mild or no depression (Table 1). And with higher H&Y stages, plasma NfL levels also elevated (Supplementary Fig. 1) (Online Resource 3). Plasma NfL levels were significantly higher for PD-MOD and PD-SD than for PD-ND, PD-MID, or controls (Fig. 1A). Area under curve (AUC) was 0.747 [95% confidence interval (CI) 0.6532–0.8399] for differentiating PD-MOD and PD-SD from PD-ND and PD-MID (Supplementary Fig. 2A) (Online Resource 4). As the results showed in Fig. 1B, we also detected remarkable difference when compared among groups of PD with anxiety. AUC was 0.721 [95% CI 0.6290–0.8128] for differentiating PD-MOA and PD-SA from PD-NA and PD-MIA

Table 1 Clinicodemographic characteristics and plasma NfL levels in healthy controls and PD patients stratified by severity of depression symptoms

Characteristic	Healthy controls	Patients with Parkinson's disease				Four group comparison *P* value
		PD-ND	PD-MID	PD-MOD	PD-SD	
n	38	24	46	27	19	
Age, yr	64.9 ± 10.6	61.1 ± 11.1	63.3 ± 10.5	69.0 ± 8.8	65.8 ± 7.5	0.059
Male	16 (42.1%)	19 (79.2%)	25 (55.3%)	13 (48.1%)	11 (57.9%)	0.067
Mean age at onset, yr	NA	58.8 ± 11.3	60.1 ± 10.5	62.0 ± 15.5	59.0 ± 10.9	0.78
Disease duration, yr	NA	2.7 ± 2.5^{b*,c*}	3.1 ± 3.5^{d**,e**}	5.2 ± 4.7^{b*,d**}	5.5 ± 4.6^{c*,e**}	0.001
LEDD, mg	NA	329 ± 153.6	353.1 ± 171.5	365 ± 178.9	444.6 ± 159.9	0.090
UPDRS-II	NA	10.3 ± 5.0^{b**,c**}	14.5 ± 8.2^{d**,e**}	24.3 ± 11.6^{b**,d**}	26.0 ± 11.6^{c**,e**}	0.000
UPDRS-III	NA	20.9 ± 11.5^{a*,b**,c**}	28.3 ± 14.5^{a*,d**,e*}	40.4 ± 14.1^{b**,d**}	37.9 ± 19.7^{c**,e*}	0.000
Hoehn and Yahr stage	NA	1.5 ± 0.8^{b**,c*}	1.7 ± 0.9^{d**,e*}	2.9 ± 1.2^{b**,d**}	2.4 ± 1.2^{c*,e*}	0.000
HAMA	NA	6.7 ± 4.8^{a**,b**,c**}	17.2 ± 11.1^{a**,d**,e**}	26.0 ± 8.0^{b**,d**,f**}	34.1 ± 7.9^{c**,e**,f**}	0.000
RBD	NA	11 (13.9%)^{b**,c**}	29 (36.7%)^{e*}	22 (27.8%)^{b**}	17 (21.5%)^{c**,e*}	0.007
PSQI	NA	6.1 ± 4.9^{a**,b**,c**}	8.8 ± 3.8^{a**,e**}	10.4 ± 5.0^{b**,f*}	13.9 ± 4.8^{c**,e**,f*}	0.0000
PDQ-39	NA	25.3 ± 18.7^{a*,b**,c**}	36.4 ± 20.3^{a*,d**,e**}	67.6 ± 27.4^{b**,d**}	46.4 ± 29.8^{c**,e**}	0.000
NfL	16.5 ± 7.3	16.2 ± 5.9^{b**,c**}	18.4 ± 9.0^{d**,e**}	32.1 ± 20.5^{b**,d**}	31.2 ± 19.7^{c**,e**}	0.000

PD, Parkinson's disease; *PD-ND*, Parkinson's disease with no depression; *PD-MID*, PD with mild depression; *PD-MOD*, PD with moderate depression; *PD-SD*, PD with severe depression; *PDQ-39*, Parkinson Disease Questionnaire 39; *LEDD*, levodopa-equivalent daily doses; *UPDRS-II/III*, Unified Parkinson's Disease Rating Scale motor examination; *RBD*, Rapid Eye Movement (REM) Sleep Behavioral Disorder; *PSQI*, Pittsburgh Sleep Quality Index; *NfL*, neurofilament light chain

Values in the same row sharing the same letter are significantly different from each other: **($p < 0.01$), *($p < 0.05$); *a* = PD-ND vs PD-MID, *b* = PD-ND vs PD-MOD, *c* = D-ND vs PD-SD, *d* = PD-MID vs PD-MOD, *e* = PD-MID vs PD-SD, *f* = PD-MOD vs PD-SD

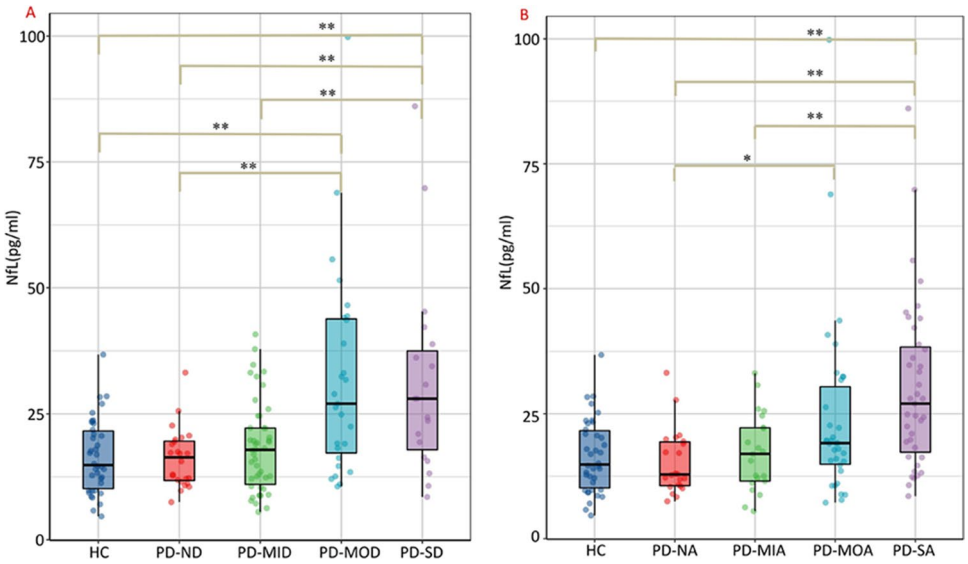

Fig. 1 Plasma concentrations of neurofilament light chain (NfL), (**A**) in healthy controls (HC) or Parkinson's disease patients with no depression (PD-ND), mild depression (PD-MID), moderate depression (PD-MOD), or severe depression (PD-SD). (**B**) In healthy controls (HC) or Parkinson's disease patients with no anxiety (PD-NA), mild anxiety (PD-MIA), moderate anxiety (PD-MOA), or severe anxiety (PD-SA). *$p<0.05$, **$p<0.01$

(Supplementary Fig. 2B) (Online Resource 4). Increased NfL levels correlated with depression severity among PD patients ($r=0.418$, 95% CI 0.252–0.554, $p<0.001$) (Supplementary Fig. 3A) (Online Resource 5). As well, plasma NfL concentration correlated positively with HAMA score ($r=0.4603$, 95% CI 0.183–0.486, $p<0.001$) (Supplementary Fig. 3B) (Online Resource 5). Binary logistic regression indicated the depression and anxiety risk was higher when NfL levels were higher (odds ratio (OR) = 1.072, $p=0.017$; OR = 1.075, $p=0.038$; respectively) (Supplementary Fig. 4) (Online Resource 6).

Discussion

As far as we are aware, this is the first study to explore the relationship of depression and anxiety in PD patients with their plasma NfL levels. We found that depression and anxiety were associated with increased plasma NfL levels in PD. Furthermore, after accounting for potential confounders such as age, mean age at PD onset, disease duration, and other non-motor symptoms, plasma NfL levels emerged as an independent risk factor for depression and anxiety.

Depression is an easily missed but common comorbidity among patients with neurodegenerative diseases, including PD. The molecular mechanisms underlying the correlation between PD and depression are complex, including neurotransmitter disturbance, reduced expression of the serotonin transporter (5-HTT), and depletion of monoaminergic neurotransmitters [7]. NfL is an sensitive indicator for reflecting white matter axonal damage in the brains, which has been observed increased in several neurologic disorders [1]. Quantification of plasma NfL concentration can not only be used in the diagnosis of PD, but also confirmed correlated with disease severity and progression in the motor and cognitive functions in PD [3]. Our results showed plasma NfL levels were significantly higher in patients with PD-SD and PD-MOD than in patients with PD-ND and PD-MID, which demonstrated that plasma NfL concentrations were also associated with depression in PD. Depression in PD has also been linked to extensive cortical degeneration involving the dorsolateral prefrontal cortex, hippocampus, anterior cingulate cortex, insula, and superior temporal gyrus [8], which may explain the increased level of NfL.

We found a similar relationship between NfL levels and anxiety among our PD patients. Depression frequently coexists with anxiety, consistent with our observation that HAMD positively correlated with HAMA ($r=0.8459$, $p<0.001$). PD involves degeneration in dopamine- and serotonin-based emotional regulation networks, which may explain the link between the two affective disorders in PD [7]. Neuroimaging studies have been shown primarily parahippocampal parts of the brain have been associated with depression, while the amygdala has been associated with anxiety; however, both brain regions typically show degeneration in PD patients [8]. Cortical degeneration associated with depression and anxiety has been linked to increased NfL levels.

In addition, our results found that PD-SD and PD-MOD showed significantly higher H&Y stages than patients with mild or no depression; same result was observed in anxiety. This suggests a relationship between depression and anxiety with disease severity in PD. Several studies reported that when compared to non-depressed ones, PD patients with depressive disorder presented more advanced H&Y stages, greater Unified Parkinson's Disease Rating Scale (UPDRS) motor, and functional impairment scores [9, 10]. This could be related to the underlying pathology of PD; depression

could be an early manifestation of the neurodegenerative process of PD and may be related with more severe and widespread neurodegeneration [10]. Furthermore, increased disease severity may be associated with the reaction to their experienced physical symptoms. Thus, depression and PD may be a bidirectional complex process, where each condition is supposed to mutually aggravate the other.

In our binary logistic regression analysis, we found Pittsburgh Sleep Quality Index (PSQI) and Parkinson's Disease Questionnaire 39 (PDQ-39) to be independent risk factors of depression. There is a relationship between poor sleep quality with anxiety and depression among patients with PD [11]. Previous work showed a negative impact of depression and anxiety on quality of life in PD [12], which we also observed here.

There are some limitations in our study. First, our sample size is limited and our study was single-center. Second, the study was not designed for longitudinal observation. Third, we did not perform an inter-group comparison between anxiety and depression. Fourth, the NfL assay is time-consuming and requires specialized equipment, so it may not be feasible in certain healthcare settings. Fifth, we used scales to evaluate depression and anxiety, which may have a subjective effect.

Despite these limitations, our study provides evidence linking increased NfL levels with depression and anxiety in PD. In fact, ROC curves showed that plasma NfL was able to differentiate between PD patients with moderate to severe depression or anxiety. Thus, NfL levels may be associated with depression severity in PD and may serve as a diagnostic biomarker of PD involving moderate to severe depression or anxiety.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10072-022-05914-2.

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Author contribution Weifang Yin, Yongyun Zhu, Baiyuan Yang, Fang Wang, Kangfu Yin, Chuanbin Zhou, Hui Ren, and Xinglong Yang participated in the conception and design of the study, data acquisition, and analysis. Weifang Yin and Yongyun Zhu were responsible for the implementation of the project, statistical analysis, and writing the first draft. Kangfu Yin and Chuanbin Zhou participated in the review and the revision of the manuscript. Baiyuan Yang and Fang Wang drafted the article and revised it. Hui Ren and Xinglong Yang revised the manuscript and made final approval of the version.

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Availability of data and material All the data was included in the present research.

Code availability Not applicable.

Declarations

Ethics approval This study was approved by the ethics committee of the First Affiliated Hospital of Kunming Medical University.

Consent to participate Written informed consent was obtained from each participant.

Consent for publication All of the authors agree to the submission of this paper.

Conflict of interest The authors declare no competing interests.

References

1. Thebault S, Booth RA, Freedman MS (2020) Blood neurofilament light chain: The neurologist's troponin? Biomedicines 8(11):523. https://doi.org/10.3390/biomedicines8110523
2. Lin Y-S, Lee W-J, Wang S-J, Fuh J-L (2018) Levels of plasma neurofilament light chain and cognitive function in patients with Alzheimer or Parkinson disease. Sci Rep 8(1):17368. https://doi.org/10.1038/s41598-018-35766-w
3. Lin CH, Li CH, Yang KC, Lin FJ, Wu CC, Chieh JJ, Chiu MJ (2019) Blood NfL: A biomarker for disease severity and progression in Parkinson disease. Neurology 93:e1104–e1111. https://doi.org/10.1212/WNL.0000000000008088
4. Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, Obeso J, Marek K et al (2015) MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord 30:1591–1601. https://doi.org/10.1002/mds.26424
5. Xiao MM, Li JB, Jiang LL, Shao H, Wang BL (2018) Plasma nesfatin-1 level is associated with severity of depression in Chinese depressive patients. BMC Psychiatry 18:88. https://doi.org/10.1186/s12888-018-1672-4
6. Cui Shi-Shuang, Juan-Juan Du, Rao Fu, Lin Yi-Qi, Huang Pei, He Ya-Chao, Gao Chao, Wang Hua-Long, Chen* Sheng-Di (2017) Prevalence and risk factors for depression and anxiety in Chinese patients with Parkinson disease. BMC Geriatr. 17(1):270. https://doi.org/10.1186/s12877-017-0666-2
7. Galts CPC, Bettio LEB, Jewett DC, Yang CC, Brocardo PS, Rodrigues ALS, Thacker JS, Gil-Mohapel J (2019) Depression in neurodegenerative diseases: common mechanisms and current treatment options. Neurosci Biobehav Rev 102:56–84. https://doi.org/10.1016/j.neubiorev.2019.04.002
8. Wen MC, Chan LL, Tan LC, Tan EK (2016) Depression, anxiety, and apathy in Parkinson's disease: insights from neuroimaging studies. Eur J Neurol 23:1001–1019. https://doi.org/10.1111/ene.13002
9. Stella F, Banzato CE, BarasneviciusQuagliato EM, Viana MA (2008) Depression in patients with Parkinson's disease: impact on functioning. J Neurol Sci 272:158–163. https://doi.org/10.1016/j.jns.2008.05.018

10. Papapetropoulos S, Ellul J, Argyriou AA, Chroni E, Lekka NP (2006) The effect of depression on motor function and disease severity of Parkinson's disease. Clin Neurol Neurosurg 108:465–469. https://doi.org/10.1016/j.clineuro.2005.08.002
11. Rana AQ, Qureshi ARM, ShamliOghli Y, Saqib Y, Mohammed B, Sarfraz Z, Rana R (2018) Decreased sleep quality in Parkinson's patients is associated with higher anxiety and depression prevalence and severity, and correlates with pain intensity and quality. Neurol Res 40:696–701. https://doi.org/10.1080/01616412.2018.1462880
12. Chuquilin-Arista F, Alvarez-Avellon T, Menendez-Gonzalez M (2020) Prevalence of depression and anxiety in Parkinson disease and impact on quality of life: a community-based study in Spain. J Geriatr Psychiatry Neurol 33:207–213. https://doi.org/10.1177/0891988719874130