Journal of Inflammation Research Dovepress

Open Access Full Text Article ORIGINAL RESEARCH

Higher Serum Galectin-3 Levels Were Associated with More Severe Motor Performance in Parkinson's Disease

Jin Xu*, Hong-Fei Yu*, Qi-Rong Wang, Lian-Chen Xiao, Yi Fang

Department of Neurology, Xiangyang Central Hospital, Affiliated Hospital of Hubei University of Arts and Science, Xiangyang, Hubei, 441021, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yi Fang; Lian-Chen Xiao, Department of Neurology, Xiangyang Central Hospital, Affiliated Hospital of Hubei University of Arts and Science, Xiangyang, People's Republic of China, Email 15997289836@163.com; lianchenhx2024@163.com

Background: Parkinson's disease (PD) is a movement disorder that lacks proven biomarkers. Case–control genome-wide association studies revealed the potential effect of galectin-3 (GAL3) on motor progression in PD patients. Based on this finding, our study aimed to explore the correlation between serum GAL3 levels and motor performance in PD patients.

Methods: Five hundred PD patients and 200 healthy controls were recruited. The serum levels of GAL3 were measured in participants by enzyme linked immunosorbent assay (ELISA). The baseline characteristics of the participants were collected, and the associated scale scores were obtained.

Results: Compared with healthy controls, the serum levels of GAL3 were greatly increased in PD patients. These levels could distinguish between PD patients and healthy controls with a sensitivity of 0.798 and a specificity of 0.815 (AUC = 0.795, 95% *CI* 0.757–0.834, $P < 0.001$). Patients with age >60 years tended to have higher serum GAL3 levels, disease duration, Hoehn-Yahr stage, MDS-UPDRS III total score, tremor subscores, rigid subscores, and bradykinesia subscores than those with age ≤60 years. When adjusting for confounders, higher GAL3 level was significantly correlated with MDS-UPDRS III total score and rigid subscores. In men with PD, GAL3 was significantly correlated with MDS-UPDRS III total score; but the association between GAL3 and bradykinesia subscores was found in women. Moreover, the associations between GAL3 with MDS-UPDRS III total score and bradykinesia subscores were significant in patients with age >60 years.

Conclusion: Higher GAL3 level was related to more severe motor performance in patients with age >60 years, and it may be a potential predictive biomarker for motor performance in PD patients.

Keywords: Parkinson's disease, Galectin-3, Motor performance, Biomarker

Introduction

Parkinson's disease (PD) is a progressive age-associated neurodegenerative disorder characterized by motor and non-motor dysfunctions.[1] Currently, L-dopa is the gold standard treatment for PD. However, the emergence of side effects, especially motor dysfunctions and dyskinesia, limits its utilization in many PD patients.[2] Mechanistically, changes in cell signaling cascades and enhanced D1 stimulation (which leads to widespread molecular adaptations in striatal medium spiny neuronal cells) are closely associated with levodopa-triggered dyskinesia.[3] Presently, the diagnosis of PD mainly depends on clinical manifestations; however, these symptoms usually occur in a progressive stage of the disorder. Therefore, it is urgent to explore validated biomarkers to diagnose and track the progression of PD.

Galectins, members of the lectin family, involve in many immunological processes, including neuroinflammation. Some researchers have reported that there were significant positive associations among Galectin-1, Galectin-9, and YKL-40 levels with cognitive performance in patients with bipolar disorder.[4] Galectin-3 (GAL3), a galactose-binding protein,

Received: 14 August 2024
Accepted: 24 October 2024
Published: 4 November 2024

has no catalytic activity and is mainly expressed in microglia of central nervous system (CNS).[5] Some researchers have demonstrated how GAL3 could be released from microglia in neuroinflammatory status and interact with different receptors, including Tlr4 and Trem2.[6] Furthermore, microglial GAL3 can be upregulated in the model of PD,[7] supporting the idea of a potential PD specific phenotype. A previous study reported that GAL3 in the outer layer of PD patients is correlated with vesicle rupture.[8] Additionally, serum GAL3 level in PD patients was significantly increased and closely associated with disease progression (Hoehn-Yahr stage).[9–11]

To the best of our knowledge, few studies have reported any correlation between serum GAL3 levels and motor performance in PD patients. Nevertheless, because of the critical role of GAL3 in the CNS, we hypothesized that abnormal GAL3 levels could be associated with motor performance. Thus, we thought that GAL3 may be associated with disease duration, Hoehn-Yahr stage, MDS-UPDRS III total score, tremor subscores, rigid subscores, and bradykinesia subscores in patients grouped by age. Therefore, our research aim was to demonstrate the correlation between serum GAL3 levels and motor performance in patients with PD.

Patients and Methods

Participants

The present study is a retrospective study, in which 500 PD inpatients and 200 healthy controls, who were evaluated by PD diagnostic criteria in China (2020 edition), were recruited at the Xiangyang Central Hospital (Xiangyang, Hubei, China), from January 2019 to May 2024. The inclusion criteria were the following: (a) the agreement to participate in this study, (b) age between 45 and 75 years, and (c) no dementia diagnosed. The patients were excluded if they had a secondary or atypical parkinsonism syndrome, malignant neoplasm, epilepsy, and severe cardiopulmonary disorder.

Demographic data, such as the age, gender, body mass index (BMI), education, duration of PD, age of onset, daily levodopa equivalent dose (LED), history of cigarette smoking, and alcohol consumption were obtained. All patients were carefully assessed by a movement disorder specialist. The Hoehn & Yahr stage scale, the Movement Disorder Society-Unified Parkinson's Disease Rating Scale part III (MDS-UPDRS III) total score were applied to all PD cases. The present study was approved by the ethics committee of the Xiangyang Central Hospital, Affiliated Hospital of Hubei University of Arts and Science (No.2024–080), and informed consent was obtained from all participants. We confirm that our study complies with the Declaration Helsinki.

High-Throughput Screening Analysis

Twenty blood samples were collected from 10 healthy individuals and 10 PD patients. Differentially expressed genes were subsequently identified by RNA-sequencing and high-throughput screening analysis (Baikede Biotechnology Co. Ltd., Wuhan, China).

Blood Sample Collection and GAL3 Quantification

In all participants, blood samples were collected from the antecubital vein, between 6.00 and 8.00 a.m. After coagulation, the samples were centrifuged at 1200 g for 5 min. Then, serum samples were collected and stored at −70°C. The serum levels of GAL3 were measured by ELISA assay. In brief, standards of GAL3, as well as serum samples, were added to microplate wells pre-coated with the respective antibodies and incubated at 37°C for 45 min. After washing five times, detection antibody was added to each well and incubated at 37°C for 30 min. Then, 1 × streptavidin-HRP conjugated antibody was added into each well and incubated at 37°C for 30 min. Finally, the reaction was terminated using a stop solution as per the manufacturer's instructions, and the absorbance values for each well were measured at 450 nm by a microplate reader.

Statistics Analysis

Statistical analyses were carried out using SPSS version 20.0 (IBM, Chicago, IL, USA). Power analysis was used to identify and eliminate outliers to improve the accuracy of data. Thus, we finally enrolled 500 PD patients and 200 healthy controls to analyze the association among GAL3 and more severe motor performance in PD. Continuous variables were

shown as mean ± standard deviation (SD) or median, and statistical significance was assessed with the Student's *t* test. Categorical data were presented as frequency (%), and statistical significance was assessed with the Fisher's exact test. The Spearman correlation analysis was utilized to evaluate the associations between GAL3 with MDS-UPDRS III and Hoehn-Yahr stage. Univariate and multivariate logistic regression analyses were used to evaluate the correlation between GAL3 and motor performance in PD patients. Receiver operating characteristic (ROC) curve was used to assess the diagnostic significance of GAL3 in PD patients. A stratified analysis was performed to further analyze the associations between GAL3 and motor performance throughout the sex and age strata. All tests were two-tailed, and a $P < 0.05$ was considered statistically significant.

Results

GAL3 Level Was Upregulated in the Blood of PD Patients

To explore the underlying therapeutic targets for PD treatment, we collected 10 blood samples from PD patients and 10 blood samples from healthy controls, to perform RNA high-throughput sequencing. The obtained heat map revealed that the differential expression of GAL3 was most significantly increased (Figures 1A). To further verify our observation, we collected additional samples from 500 PD patients and 200 healthy controls. The results in Figure 1B showed that, compared with healthy controls [(10.51±6.10) ng/mL], the levels of GAL3 in PD patients [(17.49±6.75) ng/mL] were significantly increased. ROC curve analysis suggested that GAL3 has a diagnostic significance for PD with an area under curve (AUC) of 0.795 ($P < 0.001$; 95% confidence interval [CI]: 0.757–0.843), a sensitivity of 0.798, and a specificity of 0.815 (Figure 1C). In addition, GAL3 was significantly and positively associated with the Hoehn-Yahr stage and the UPDRS III and (Figure 1D and E).

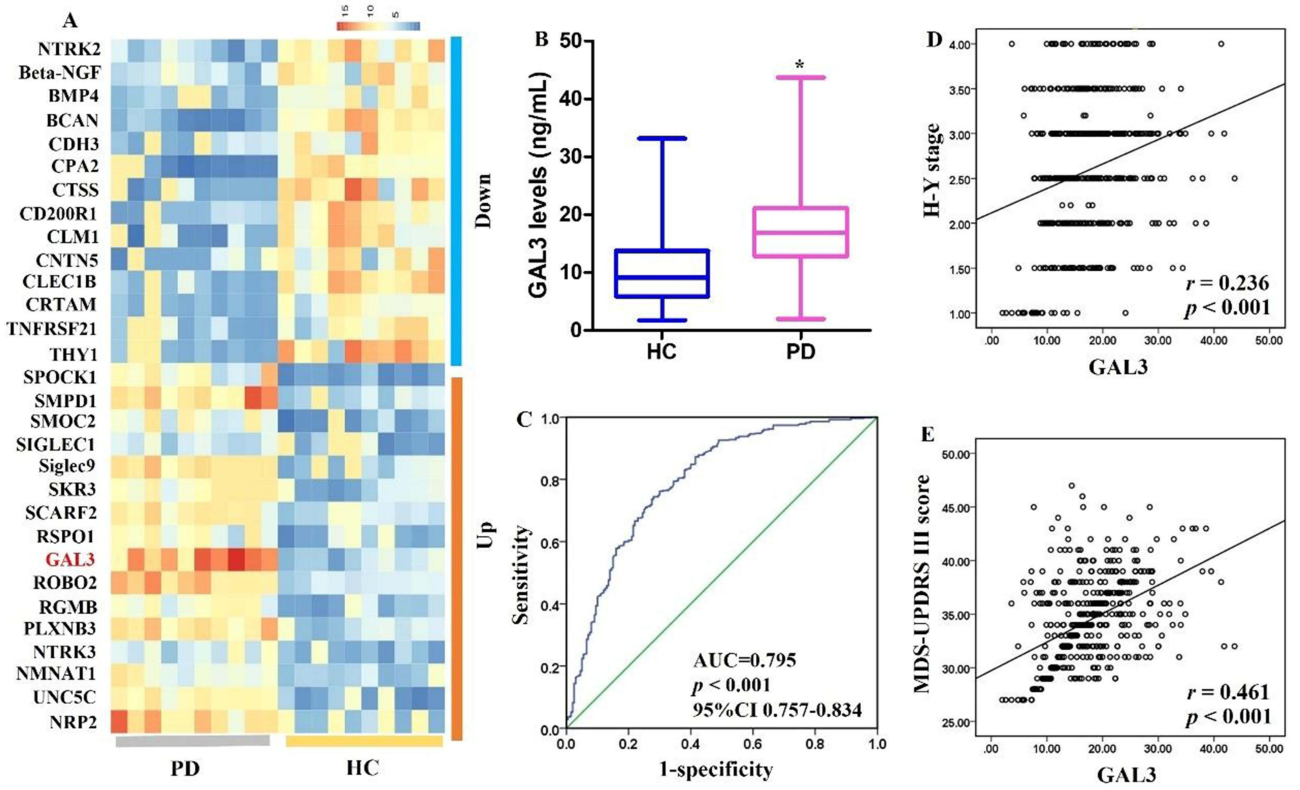

Figure 1 GAL3 levels increase in PD patients. (**A**) Differential gene expression between healthy controls and PD patients. (**B**) Serum GAL3 levels in PD patients were higher than healthy controls. (**C**) ROC curve for GAL3 to diagnose PD. (**D**) Correlation analysis among serum GAL3 and Hoehn-Yahr stage. (**E**) Correlation analysis between serum GAL3 and MDS-UPDRS III score. * *P* <0.05, compared with HC group.

Abbreviations: HC, healthy controls; PD, Parkinson's disease; GAL3, Galectin-3; H-Y stage, Hoehn-Yahr stage.

Baseline Characteristics of PD Patients

A total of 500 PD cases were divided into two groups, including patients with ≤60 years (n = 214) and with >60 years (n = 286). The baseline characteristics are shown in Table 1. The average of PD patients was 61.3 ± 6.0 years, the median disease duration was 6.2 years, the median age of PD onset was 57 years, and 58.8% were female. There were no significant age-specific differences in BMI, education, alcohol status, cigarette smoking, gait/postural subscores, and LEED. Moreover, males with higher disease duration, Hoehn-Yahr stage, MDS-UPDRS III total score, tremor subscores, rigid subscores, bradykinesia subscores, and GAL3 levels were detected in patients with >60 years, relative to patients with ≤60 years.

Motor Performance and GAL3 Levels in PD Patients

The univariate linear regression model revealed that higher serum GAL3 level was significantly correlated with MDS-UPDRS III total score, tremor subscores, rigid subscores, and bradykinesia subscores ($P < 0.05$, Table 2). The multivariable analysis (model 1 and 2) demonstrated that higher serum GAL3 level was significantly correlated with MDS-UPDRS III total score and rigid subscores ($P < 0.05$); no significant correlation was found between GAL3 and tremor and bradykinesia subscores in the two models. Serum GAL3 level was significantly associated with bradykinesia subscores in model 1, but not in model 2.

Motor Performance and GAL3 Levels in PD Patients, Grouped by Sex

The univariate linear regression model displayed that higher GAL3 level was significantly correlated with MDS-UPDRS III score and tremor subscores in men, whereas only associations between GAL3 and MDS-UPDRS III score were found

Table 1 Characteristics of PD Patients Grouped by Age

Variables	Total (n = 500)	≤ 60 years (n = 214)	> 60 years (n = 286)	*p*-value
Gender				0.015
Male	206 (41.2%)	83 (38.8%)	127 (44.4%)	
Female	294 (58.8%)	131 (61.2%)	159 (55.6%)	
Age (years)	61.3 ± 6.0	54.7 ± 5.9	66.2 ± 6.1	0.014
BMI (kg/m^2)	21.8 ± 3.4	21.7 ± 3.2	21.8 ± 3.5	0.892
Education				0.415
Primary school	108 (21.6%)	55 (25.7%)	53 (18.5%)	
Middle school	90 (18.0%)	38 (17.7%)	52 (18.2%)	
High school	145 (29.0%)	56 (26.2%)	89 (31.1%)	
University	157 (31.4%)	65 (30.4%)	92 (32.2%)	
Alcohol status				0.209
Yes	218 (43.6%)	98 (45.8%)	120 (42.9%)	
No	282 (56.4%)	116 (54.2%)	166 (58.0%)	
Cigarette smoking				0.552
Yes	97 (19.4%)	45 (21.0%)	52 (18.2%)	
No	403 (80.6%)	169 (79.0%)	234 (81.8%)	
Age of onset (years)	57 (49, 64)	54 (49, 59)	59 (50, 64)	0.087
Disease duration (years)	6.2 (1, 11)	4.7 (1, 9)	7.3 (2, 11)	0.012
Hoehn-Yahr stage	2.5 (1.0, 4.0)	2.0 (1.0, 3.0)	3.0 (1.0, 4.0)	0.009
MDS-UPDRS III total score	34 (27, 47)	31 (27, 43)	36 (29, 47)	0.016
Tremor subscores	6.0 (2.0, 11.0)	5.0 (2.0, 10.0)	7.0 (3.0, 11.0)	0.006
Rigid subscores	8.0 (4.0, 10.0)	7.0 (4.0, 10.0)	8.5 (4.0, 10.0)	0.037
Bradykinesia subscores	25.0 (13.0, 32.0)	23.0 (13.0, 32.0)	27 (13.0, 32.0)	0.018
Gait/postural subscores	4.0 (1.5, 7.0)	4.0 (1.5, 7.0)	4.0 (2.0, 7.0)	0.318
LEED (mg/day)	399.0 (200.0, 530.0)	388 (200.0, 510.0)	407 (220.0, 530.0)	0.095
GAL3 (ng/mL)	17.49 ± 6.75	15.51 ± 6.28	18.98 ± 6.71	<0.001

Abbreviations: BMI, body mass index; LEED, levodopa equivalent daily dosage; GAL3, Galectin-3.

Table 2 Motor Performance Based on GAL3 Levels, Total Study Population

Variables	Univariate		Model 1		Model 2	
	B coefficient (95% CI)	*P*	*B* coefficient (95% CI)	*P*	*B* coefficient (95% CI)	*P*
MDS-UPDRS III score	4.127 (1.271, 10.974)	0.007	1.095 (1.009, 4.166)	0.013	0.874 (0.025, 0.997)	0.022
Tremor subscores	0.718 (0.016, 0.908)	0.016	0.651 (0.106, 1.972)	0.317	0.196 (0.068, 2.008)	0.573
Rigid subscores	1.285 (1.006, 5.117)	0.035	1.612 (1.051, 4.123)	0.042	1.218 (1.053, 4.015)	0.046
Bradykinesia subscores	2.967 (1.002, 8.424)	0.029	2.186 (1.527, 6.109)	0.037	1.996 (0.609, 3.227)	0.424
Gait/postural subscores	0.775 (0.017, 2.109)	0.332	0.564 (0.185, 1.278)	0.451	0.551 (0.274, 1.331)	0.448

Notes: Multivariable linear regression model 1 was adjusted for age, gender, BMI, education, alcohol status, and cigarette smoking; model 2 was further adjusted for age of onset, disease duration, Hoehn-Yahr stage, LEED.

in model 1 and model 2 (all $P < 0.05$, Table 3). There were no significant correlations among GAL3 with rigid subscores, bradykinesia subscores, and gait/postural subscores in men (all $P > 0.05$). In women, we reported that higher GAL3 level was significantly correlated with MDS-UPDRS III score, rigid subscores, and bradykinesia subscores in univariate analysis model (all $P < 0.05$); the associations among GAL3 with rigid subscores and bradykinesia subscores were found in model 1 (all $P < 0.05$); and only a relationship between GAL3 and bradykinesia subscores was found in model 2 ($P < 0.05$). Moreover, there were no significant associations between GAL3 and tremor subscores and gait/postural subscores were reported ($P > 0.05$).

Motor Performance and GAL3 Levels in PD Patients, Grouped by Age

The univariate linear regression model demonstrated that higher GAL3 level was significantly correlated with tremor subscores in patients with age ≤60 years, whereas the same association was found in model 1 (all $P < 0.05$, Table 4). There were no significant correlations among GAL3 with MDS-UPDRS III score, bradykinesia subscores, and gait/postural subscores in patients with age ≤60 years (all $P > 0.05$). In patients with age >60 years, we found that higher GAL3 level was significantly correlated with MDS-UPDRS III score, tremor subscores, and bradykinesia subscores in univariate analysis model (all $P < 0.05$); the associations among GAL3 with MDS-UPDRS III score, tremor subscores and bradykinesia subscores were found in model 1 (all $P < 0.05$); and the relationships between GAL3 and MDS-UPDRS III score and bradykinesia subscores were found in model 2 ($P < 0.05$). Moreover, there were no significant associations between GAL3 and rigid subscores and gait/postural subscores were reported ($P > 0.05$).

Table 3 Motor Performance Based on GAL3 Levels by Sex

Variables	Univariate		Model 1		Model 2	
	B coefficient (95% CI)	*P*	*B* coefficient (95% CI)	*P*	*B* coefficient (95% CI)	*P*
Males						
MDS-UPDRS III score	4.103 (1.315, 14.715)	0.025	0.537 (0.117, 0.918)	0.034	0.712 (0.129, 0.996)	0.048
Tremor subscores	1.826 (1.164, 5.108)	0.044	3.217 (0.516, 9.664)	0.164	0.382 (0.135, 7.265)	0.395
Rigid subscores	0.725 (0.173, 4.093)	0.317	1.076 (0.103, 6.228)	0.447	2.351 (0.816, 4.119)	0.616
Bradykinesia subscores	2.108 (0.716, 7.119)	0.572	1.082 (0.195, 7.298)	0.612	1.073 (0.771, 6.527)	0.775
Gait/postural subscores	0.915 (0.285, 4.108)	0.527	2.053 (0.359, 9.165)	0.765	1.039 (0.967, 4.016)	0.683
Females						
MDS-UPDRS III score	2.365 (1.673, 11.096)	0.015	2.018 (0.701, 10.716)	0.872	3.028 (0.107, 11.265)	0.815
Tremor subscores	3.482 (0.226, 7.883)	0.736	1.437 (0.631, 7.118)	0.521	2.672 (0.926, 8.115)	0.429
Rigid subscores	3.087 (1.117, 8.264)	0.033	3.042 (1.227, 5.094)	0.041	3.005 (0.437, 6.273)	0.873
Bradykinesia subscores	1.273 (1.034, 6.773)	0.011	4.076 (1.673, 19.163)	0.026	3.484 (1.983, 17.229)	0.043
Gait/postural subscores	1.226 (0.964, 2.745)	0.746	1.063 (0.673, 4.894)	0.648	1.211 (0.273, 4.085)	0.401

Notes: Multivariable linear regression model 1 was adjusted for age, gender, BMI, education, alcohol status, and cigarette smoking; model 2 was further adjusted for age of onset, disease duration, Hoehn-Yahr stage, LEED.

Table 4 Motor Performance Based on GAL3 Levels by Age

Variables	Univariate		Model 1		Model 2	
	B coefficient (95% CI)	*P*	*B* coefficient (95% CI)	*P*	*B* coefficient (95% CI)	*P*
Age ≤ 60 years						
MDS-UPDRS III score	3.197 (−4.092, 6.921)	0.417	0.065 (−8.236, 14.218)	0.572	0.093 (−6.172, 16.109)	0.418
Tremor subscores	−1.905 (−3.006, −0.762)	0.018	−2.618 (−9.024, −0.328)	0.043	−2.011 (−8.227, 0.014)	0.059
Rigid subscores	0.811 (−7.021, 6.169)	0.517	0.017 (−2.073, 3.387)	0.448	0.009 (−2.091, 2.782)	0.519
Bradykinesia subscores	2.185 (−0.215, 8.015)	0.661	−0.016 (−12.663, 10.926)	0.892	−0.011 (−13.093, 8.925)	0.736
Gait/postural subscores	−2.107 (−8.002, 0.916)	0.097	0.216 (−0.452, 6.917)	0.093	0.175 (−0.318, 5.119)	0.154
Age > 60 years						
MDS-UPDRS III score	−2.017 (−7.192, −0.153)	0.012	−3.452 (−8.152, −0.946)	0.032	−3.659 (−9.016, −1.072)	0.048
Tremor subscores	−0.617 (−2.018, −0.107)	0.026	−1.746 (−7.093, −0.073)	0.047	−2.009 (−6.825, 0.068)	0.085
Rigid subscores	0.423 (−3.187, 1.783)	0.412	−0.019 (−10.632, 8.904)	0.648	−0.014 (−12.772, 10.196)	0.725
Bradykinesia subscores	−1.826 (−4.118, −0.259)	0.009	−0.946 (−3.817, −0.126)	0.018	−0.628 (−4.092, −0.104)	0.042
Gait/postural subscores	−0.652 (−1.572, 0.994)	0.516	0.043 (−6.924, 9.117)	0.473	0.032 (−7.163, 3.449)	0.732

Notes: Multivariable linear regression model 1 was adjusted for age, gender, BMI, education, alcohol status, and cigarette smoking; model 2 was further adjusted for age of onset, disease duration, Hoehn-Yahr stage, LEED.

Discussion

By performing high-throughput RNA sequencing, our study found that the differential expression of GAL3 in PD patients was significantly increased in comparison with healthy controls. Moreover, there was an association between GAL3 serum levels and motor performance in PD patients. The relationship between GAL3 levels and motor performance remained significant after adjusting for some potential confounding factors. We also found that PD patients with higher serum levels of GAL3 are more likely to be older.

Cardinal motor symptoms, such as resting tremor, rigidity, bradykinesia, and gait/postural instability, are usually the initial presentation and seriously affect the daily activities of patients.[12] Due to the negative impact of dyskinesia on the treatment of PD and quality of life, therapeutic methods for preventing dyskinesia are needed, such as the identification of its risk factors. Previous studies have reported that several risk factors were demonstrated to be related to the development of dyskinesia. Those factors include the age of disease onset, the duration of PD, male/female gender, and the levodopa treatment dose.[13–15] The present research demonstrated that PD patients with age >60 years tended to have a longer disease duration, higher Hoehn-Yahr stage, MDS-UPDRS III total score, tremor subscores, rigid subscores, bradykinesia subscores, and GAL3 levels than those with age ≤60 years.

GAL3 was further demonstrated to be closely associated with extracellular amyloid and intracellular tau aggregates.[16] These findings indicate that GAL3 may play a role in amyloid fibril formation, a pathological biomarker of human neurodegenerative diseases, including PD. A cause role of GAL3 in PD is reported by a recent study, which demonstrated that the single nucleotide polymorphisms in GAL3 gene were correlated with an increased risk of PD.[17] Our study also revealed a higher risk of patients aged >60 years experiencing worse motor performance when compared to those aged ≤60 years. PD is recognized as age-related, with an increased risk associated with aging.[18] Our study reported that higher GAL3 level was associated with worse motor performance in PD patients, which was similar to previous results, which indicated that GAL3 may be a participant in the pathogenesis of PD.

Although the mechanisms by which GAL3 involves in the development of PD and worse motor performance are not fully demonstrated, the function of GAL3 makes it biologically plausible. A previous study revealed an important role for GAL3 in the aggregation process of α-synuclein and the formation of Lewy bodies, resulting in the production of harmful strains, which induces neuronal degeneration in PD model.[19] These findings suggested that pharmacological targeting of GAL3 appears as a promising preclinical strategy to overcome PD-related pathology. In addition, serum GAL3 was reported to be a potential noninvasive biomarker for identifying PD,[9] our data also suggested GAL3 can distinguish between PD patients and healthy controls with a sensitivity of 0.798 and a specificity of 0.815. Aging can contribute to a decline in motor performance, possibly due to changes in central brain areas.[20] Moreover, the associations between

GAL3 with MDS-UPDRS III total score and bradykinesia subscores were significant in patients with age >60 years, suggesting that age affects motor performance in PD patients. Our observation has some limitations. First, due to the cross-sectional nature of the study, we were unable to establish a causal relationship between serum GAL3 levels and motor performance in PD patients. Second, the relatively small sample size suggests that larger, multi-center studies are needed to validate our findings. In the future study, we will explore the action mechanism of GAL3 in the pathogenesis of PD in animal models.

Conclusion

In summary, we revealed that higher serum GAL3 level is positively correlated with worse motor performance in PD patients. Considering the confounding factors, multivariate regression analysis indicated that age-specific effect of GAL3 level on MDS-UPDRS III score and bradykinesia subscores indicate different mechanisms underlying motor performance in PD patients at different ages.

Data Sharing Statement

The dataset used in the preparation of this study will be available from the corresponding author upon reasonable request.

Acknowledgments

The authors would like to express their gratitude to EditSprings (https://www.editsprings.cn) for the expert linguistic services provided.

Disclosure

The authors declare that they have no conflict of interest for this work.

References

1. Tolosa E, Garrido A, Scholz SW, Poewe W. Challenges in the diagnosis of Parkinson's disease. *Lancet Neurol*. 2021;20(5):385–397. doi:10.1016/S1474-4422(21)00030-2
2. Paul R, Borah A. L-DOPA-induced hyperhomocysteinemia in Parkinson's disease: elephant in the room. *Biochim Biophys Acta*. 2016;1860(9):1989–1997. doi:10.1016/j.bbagen.2016.06.018
3. Kwon DK, Kwatra M, Wang J, Ko HSL. induced dyskinesia in Parkinson's disease: pathogenesis and emerging treatment strategies. *Cells*. 2022;11(23):3736. doi:10.3390/cells11233736
4. Selahaddin E, Bahadir D, Sengul S, et al. Galectin-9, and YKL-40 levels in bipolar disorder and their relationship with cognitive functions. *Brain Behav*. 14(2):e3421. doi:10.1002/brb3.3421
5. Soares LC, Al-Dalahmah O, Hillis J, et al. Novel galectin-3 roles in neurogenesis, inflammation and neurological diseases. *Cells*. 2021;10(11):3047. doi:10.3390/cells10113047
6. Boza-Serrano A, Ruiz R, Sanchez-Varo R, Garcia-Revilla J, Yang J-FI. Galectin-3, a novel endogenous REM2 ligand, detrimentally regulates inflammatory response in Alzheimer's disease. *Acta Neuropathol*. 2019;138:251–273. doi:10.1007/s00401-019-02013-z
7. Garcia-Dominguez I, Vesela K, Garcia-Revilla J, Carrillo-Jimenez A, Roca-Ceballos MA, Santiago M. Peripheral inflammation enhances microglia response and nigral dopaminergic cell death in an in vivo MPTP model of Parkinson's disease. *Front Cell Neurosci*. 2018;12:398. doi:10.3389/fncel.2018.00398
8. Flavin WP, Bousset L, Green ZC, Chu Y, Skarpathiotis S, Chaney MJ. Endocytic vesicle rupture is a conserved mechanism of cellular invasion by amyloid proteins. *Acta Neuropathol*. 2017;134:629–653. doi:10.1007/s00401-017-1722-x
9. Cengiz T, Turkboyları S, Gencler OS, Anlar O. The roles of galectin-3 and galectin-4 in the idiopatic Parkinson disease and its progression. *Clin Neurol Neurosurg*. 2019;184:105373. doi:10.1016/j.clineuro.2019.105373
10. Yazar HO, Yazar T, Cihan M. A preliminary data: evaluation of serum galectin-3 levels in patients with idiopathic Parkinson's disease. *J Clin Neurosci*. 2019;70:164–168. doi:10.1016/j.jocn.2019.08.032
11. Wu HC, Chang KH, Chiang MC, Chen CM. Alterations of plasma galectin-3 and C3 levels in patients with Parkinson's disease. *Brain Sci*. 2021;11(11):1515. doi:10.3390/brainsci11111515
12. Todorova A, Jenner P, Ray Chaudhuri K. Non-motor Parkinson's: integral to motor Parkinson's, yet often neglected. *Pract Neurol*. 2014;14(5):310–322. doi:10.1136/practneurol-2013-000741
13. Politis M. Dyskinesias after neural transplantation in Parkinson's disease: what do we know and what is next? *BMC Med*. 2010;8:80. doi:10.1186/1741-7015-8-80
14. Donzuso G, Agosta F, Canu E, Filippi M. MRI of motor and nonmotor therapy-induced complications in Parkinson's disease. *Mov Disord*. 2020;35(5):724–740. doi:10.1002/mds.28025
15. Wang M, Wang W, Gao Z, et al. Dyskinesia-hyperpyrexia syndrome in Parkinson's disease: a systematic review. *Clin Auton Res*. 2021;31(4):529–542. doi:10.1007/s10286-021-00801-w

16. Srejovic I, Selakovic D, Jovicic N, Jakovljević V, Lukic ML, Rosic G. Galectin-3: roles in neurodevelopment, neuroinflammation, and behavior. *Biomolecules*. 2020;10(5):798. doi:10.3390/biom10050798
17. Billingsley KJ, Barbosa IA, Bandres-Ciga S, Quinn JP, Bubb VJ, Deshpande C. Mitochondria function associated genes contribute to Parkinson's disease risk and later age at onset. *NPJ Parkinsons Dis*. 2019;5:8. doi:10.1038/s41531-019-0080-x
18. Lenka A, Padmakumar C, Pal PK. Treatment of older Parkinson's disease. *Int Rev Neurobiol*. 2017;132:381–405.
19. García-Revilla J, Boza-Serrano A, Jin Y, et al. Galectin-3 shapes toxic alpha-synuclein strains in Parkinson's disease. *Acta Neuropathol*. 2023;146(1):51–75. doi:10.1007/s00401-023-02585-x
20. Doty RL, Kamath V. The influences of age on olfaction: a review. *Front Psychol*. 2014;5:20. doi:10.3389/fpsyg.2014.00020