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The efficacy of levodopa/carbidopa/entacapone on cognitive function in moderate to advanced Parkinson's disease and its relationship with peripheral inflammatory cytokines

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Abstract

Background Entacapone has been widely used in the treatment of moderate to advanced Parkinson's disease (PD), and its efficacy for motor symptoms has been well-known from several clinical trials and long-term clinical use. The efficacy of Levodopa/Carbidopa/Entacapone (LCE) on neuropsychological functions in moderate to advanced PD has not been validated yet, and little is known about the effect of LCE on peripheral inflammatory cytokines.

Objectives The aim of this study was to investigate the efficacy of LCE on neuropsychological functions in moderate to advanced PD and to explore its relationship with the changes in peripheral inflammatory cytokine levels.

Methods All patients were randomly assigned to the experimental group receiving treatment of LCE or the control group receiving treatment of Levodopa/Carbidopa (LC). All patients were clinically evaluated using the Unified Parkinson's Disease Rating Scale part III (UPDRS III), the total score of the Parkinson's Disease Questionnaire-39 (PDQ-39), the Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA), the Hamilton Anxiety Scale (HAMA), and the Hamilton Depression Scale (HAMD), and serum homocysteine (HCY) as well as serum inflammatory cytokines were measured at baseline and after 8 weeks.

Results The moderate to advanced PD patients treated with LCE had more significant improvement in MMSE scores ($P=0.004$) and MoCA scores ($P=0.001$), as well as a greater decline in IL-6 levels ($P=0.002$) than those treated with LC. There were no significant differences in the changes of the UPDRS III, PDQ39, HAMA, and HAMD scores between the two treatment groups. Linear correlation analysis revealed that there was a significant negative correlation between the improvement of MoCA scores (ΔMoCA) and the reduction of IL-6 levels (ΔIL-6) (correlation coefficient: -0.252; $P=0.024$).

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Conclusions The ability of LCE to improve cognitive function and to downregulate the peripheral inflammatory cytokine IL-6 levels in moderate to advanced PD is superior to the traditional dopamine preparation—LC. LCE may improve cognitive function by suppressing the levels of inflammatory cytokines like IL-6.

Trial registration The full name of the registry: Dongyang People's Hospital, Affiliated to Wenzhou Medical University. The trial registration number (TRN): ChiCTR2400091631. The date of registration: October 31, 2024 (Retrospectively registered).

Keywords Levodopa/carbidopa/entacapone, Moderate to advanced Parkinson's disease, Cognitive function, Peripheral inflammatory cytokines

Introduction

As the most common neurodegenerative movement disorder, Parkinson's disease (PD) is characterized by typical motor symptoms such as bradykinesia, rigidity, rest tremor, posture instability, and gait disorder [1]. It places a burden on more than 10 million people worldwide, and its prevalence is expected to increase with the aging population [2]. The moderate to advanced PD patients experience more severe motor impairment, various non-motor symptoms, and motor fluctuations. While levodopa remains the gold standard of symptomatic efficacy in the drug treatment of PD, it becomes problematic in moderate to advanced PD patients due to the duration of LD efficacy that is shortened with time, as well as increased motor complications [3].

Fortunately, motor fluctuations can be improved by the addition of other anti-Parkinson drugs [3]. Levodopa/Carbidopa/entacapone (LCE) is a levodopa agent that combines both a dopa decarboxylase (DDC) inhibitor and a catechol O-methyltransferase (COMT) inhibitor, which can extend the serum levodopa half-life and allow more levodopa to enter the brain over a longer period of time, suggesting a potential suitability for use in moderate to advanced PD compared to the traditional dopamine preparation—Levodopa/Carbidopa (LC) [4]. While entacapone has been widely used in clinical practice for moderate to advanced PD, and the efficacy for motor symptoms has been well known. The efficacy of LCE on neuropsychological functions of moderate to advanced PD patients remains to be evaluated.

Previous studies have demonstrated that the immune-inflammatory response plays an important role in driving neurodegenerative disease [5], and it is a potential mechanism involved in PD origin or progression [6, 7]. The over-activation of microglial cells induced by the protein alpha-synuclein in the brains of PD patients could lead to an increased release of pro-inflammatory cytokines, including tumor necrosis factor (TNF)-α, interleukin (IL)-6, and interleukin (IFN)-γ [8, 9], which are closely related to the severity and prognosis of PD [10, 11]. Previous studies have revealed that patients with inflammatory bowel disease have a higher risk of developing PD [12]. This suggests that systemic inflammation plays an important role in PD neurodegeneration [13]. A recent study has demonstrated that the COMT inhibitor can boost anti-inflammatory activity by suppressing the expression of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6 [14]. The relationship between the efficacy of LCE and the changes in peripheral inflammatory cytokine levels has not been adequately studied but attracted our attention.

Therefore, we conducted this study to ascertain the clinical efficacy of LCE on neuropsychological functions, focusing on cognitive function in moderate to advanced PD patients, and to explore the relationship between the efficacy and the changes of peripheral inflammatory cytokine levels.

Materials and methods

Participants

Patients aged 45 to 85 who met the MDS Clinical Diagnostic Criteria for Parkinson's Disease [1] were enrolled from April 2021 to April 2023. According to the severity of the movement disorders, patients with Hoehn-Yahr stage greater than 2.5 were identified as "moderate and advanced" PD patients [15]. Patients who had a history of dementia, major anxiety, major depression, or were taking related medication, with recent infections, immune system diseases, malignant tumors, taking immunosuppressive drugs or COMT inhibitors before enrollment, poor treatment compliance, and those with incomplete clinical data were excluded. This study was approved by the ethics committee of the Dongyang Affiliated Hospital of Wenzhou Medical University (Ethic ID: 2021-YX-037). All participants signed written informed consents.

Therapeutic methods

This was an 8-week, monocentric, small sample, open-label randomized controlled study to compare the efficacy of LCE with LC in moderate to advanced PD patients, which adheres to CONSORT guidelines. We estimated the sample size based on previous similar studies in this field and preliminarily decided that the sample size of the study was 400 [16]. Patients were randomly allocated into two groups using the random number table method: the experimental group treated with LCE

and the control group treated with LC. For PD patients previously treated with LC, we transferred to LCE using levodopa equivalent dose (LED) replacement titration method. For example, one tablet of LCE contains levodopa 100 mg, carbidopa 25 mg, and entacapone 200 mg, which converted to LED is 133 mg. One tablet of LC contains levodopa 200 mg and carbidopa 50 mg, which converted to LED is 200 mg. That is, 1.5 pieces of LCE were used to replace the original 1 piece of LC.

Clinical assessments

Baseline assessments included gender, age, disease duration, and medication history. The LEDDs given to each PD patient were calculated, which is according to the LED conversion formulae reported by Tomlinson CL, et al. [17]. At baseline and the 8-week follow-up visit, each PD patient was assessed with standardized instruments including the Unified Parkinson's Disease Rating Scale part III (UPDRS III) [18], the total score of Parkinson's Disease Questionnaire-39 item version (PDQ-39) [19], the Mini-Mental State Examination (MMSE) [20], the Montreal Cognitive Assessment (MoCA) [21], the Hamilton Anxiety Scale (HAMA) [22], and the Hamilton Depression Scale (HAMD) [23]. All of the above assessments were performed by two professional blinded raters, who were blinded to the patients' medication or dosing information and the results of blood test results.

Detecting serum inflammatory cytokines

Venous blood samples were collected from the participants at baseline and after 8 weeks and allowed to naturally clot at room temperature for a minimum of 30 min. Afterward, the samples were centrifuged at 1,000 rpm for 10 min, and the separated serum was sent for testing or stored in 200-μL aliquots at -20 °C until further analysis. To assess inflammation levels, a panel of key inflammation-related markers, including the human inflammatory panel 1 (IL-4, IL-6, IL-10, IL-17, TNF-α, and IFN-γ), was measured using a multiple microsphere flow immunofluorescence assay method. The clinical laboratory conducts specific procedures for cytokine determination following the instructions provided by the manufacturer for the reagents, as outlined in the supplementary materials.

Table 1 General characteristics between the experimental group and the control group

Characteristic	Experimental group ($n=40$)	Control group ($n=40$)	*P*
Gender(male/female)	22/18	21/19	0.823[a]
Age(years)	70.0(63.3–74.0)	72.5(64.3–76.0)	0.335[b]
Disease duration(years)	6.0(3.0–8.0)	5.0(3.1-8.0)	0.298[b]
H-Y stage	3.5(3.0–4.0)	3.5(3.0–4.0)	0.387[b]
LEDDs(mg/d)	474.0(399.0-499.0)	450.0(356.3-593.8)	0.954[b]
DAs	18/22	30/10	0.006[a]
MAOBI	13/27	20/20	0.112[a]
Other anti-PD drugs	0/40	4/36	0.124[a]

LEDDs, Levodopa-equivalent daily doses; H-Y, Hoehn-Yahr; DAs: dopamine agonists, MAO-BI: monoamine oxidase type-B inhibitor, Other anti-PD drugs include amantadine, anticholinergic drugs

Data was presented as median (IQR). [a] indicates Chi-square test; [b] indicates independent samples Mann-Whitney U test. $p<0.05$ was considered statistically significant

Statistical analysis

Statistical analyses of clinical/demographic variables were performed using Student t-tests for normally distributed continuous variables or Mann-Whitney U tests for non-normally distributed continuous variables. The Kolmogorov-Smirnov test was employed to assess the normality of the data. A p-value greater than 0.05, corresponding to the test statistic, indicates that the data follows a normal distribution. Chi-square tests were used for categorical variables. Within-group comparisons of data before and after treatment were analyzed using paired t-tests or paired Mann-Whitney U tests. For the repeated single-factor analysis, we applied Bonferroni correction, and the difference was considered statistically significant at $p<0.025$. Multivariate analysis of covariance (ANCOVA) with group as an independent factor was conducted to evaluate the effect of treatment on the change of clinical assessment from baseline. Correlations between clinical scores and inflammatory cytokine levels were analyzed using Spearman correlation coefficients. Multiple linear regression analysis was performed to evaluate the effect of cytokine alterations on the change of clinical scores. All statistical tests were conducted against a two-sided alternative hypothesis employing a significance level of 0.05 unless otherwise noted. IBM SPSS Statistics, version 25.0 (IBM Corp., Armonk, NY, USA) was used in the current study.

Results

Demographic characteristics

A total of 96 PD patients, meeting the specified inclusion criteria, were randomized into two treatment groups. During the follow-up period, 7 patients from the experimental group and 9 from the control group were lost; a flow chart detailing the lost cases can be found in Supplementary Materials Fig. 1. Consequently, a total of 80 PD patients, ranging in age from 45 to 85 years were enrolled, including 40 PD patients in the experimental group treated with LCE and 40 PD patients in the control group treated with LC. Demographic and baseline characteristics are presented in Table 1. At baseline, there were no significant differences observed between the two groups concerning gender, age, disease duration, LEDDs, or H-Y stage. A notable difference was observed in the

Table 2 Comparison of UPDRS III and PDQ-39 scores before and after treatment

Group	UPDRS III score		P2	PDQ-39 score		P3
	Before treatment	After treatment		Before treatment	After treatment	
Experimental group ($n=40$)	47.5(39.0-59.3)	36.5(27.3–43.8)	<0.001[a]	47.5(32.5–66.3)	36.0(23.0-52.3)	<0.001[a]
Control group ($n=40$)	52.0(39.5–62.8)	39.0(34.0-48.8)	<0.001[a]	48.5(39.8–67.0)	40.5(32.3–48.0)	<0.001[a]
P1	0.402[b]	0.027[b]		0.430[b]	0.134[b]	

UPDRS III, Unified Parkinson's Disease Rating Scale part III; PDQ-39, The Parkinson's Disease Questionnaire 39; Data was presented as median (IQR). [a] indicates paired Mann-Whitney U test; [b] indicates independent samples Mann-Whitney U test. After correction by Bonferroni, $p<0.025$ was considered statistically significant

P1, p-value for comparison between the two groups. P2, P3, p-value for comparison before and after treatment within group

Table 3 Comparison of MMSE and MoCA scores before and after treatment

Group	MMSE score		P2	MoCA score		P3
	Before treatment	After treatment		Before treatment	After treatment	
Experimental group ($n=40$)	26.5(23.0-28.8)	26.0(23.3–29.0)	0.202[a]	20.0 (17.0-23.5)	21.5(19.0–25.0)	<0.001[a]
Control group ($n=40$)	25.0(22.0–28.0)	24.0(22.0–27.0)	0.414[a]	19.0 (16.3–22.0)	18.5(16.0-21.8)	0.296[a]
P1	0.285[b]	0.038[b]		0.446[b]	<0.001[b]	

MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment

Data was presented as median (IQR). [a] indicates paired Mann-Whitney U test; [b] indicates independent samples Mann-Whitney U test. After correction by Bonferroni, $p<0.025$ was considered statistically significant

P1, p-value for comparison between the two groups. P2, P3, p-value for comparison before and after treatment within group

Table 4 Comparison of HAMA and HAMD scores before and after treatment

Group	HAMA score		P2	HAMD score		P3
	Before treatment	After treatment		Before treatment	After treatment	
Experimental group ($n=40$)	10.0(6.0–13.0)	7.0(5.0–10.0)	0.064[a]	6.0(4.0–12.0)	5.0(2.0-8.8)	0.083[a]
Control group ($n=40$)	8.0(4.0-14.8)	9.0(4.3–14.0)	0.720[a]	8.5(4.3–13.0)	6.0(2.3–13.8)	0.054[a]
P1	0.424[b]	0.393[b]		0.619[b]	0.530[b]	

HAMA, The Hamilton Anxiety Scale; HAMD, The Hamilton Depression Scale

Data was presented as median (IQR). [a] indicates paired Mann-Whitney U test; [b] indicates independent samples Mann-Whitney U test. After correction by Bonferroni, $p<0.025$ was considered statistically significant

P1, p-value for comparison between the two groups. P2, P3, p-value for comparison before and after treatment within group

utilization of dopamine agonists (DAs) between the two groups of PD patients ($P=0.006$); see Table 1 for details.

Comparison of UPDRS III and PDQ-39 scores between the groups

Table 2 illustrates that following an eight-week treatment period, both the experimental group and control group exhibited notable reductions in UPDRS III and PDQ-39 scores ($P<0.001$), and the experimental group demonstrated a significantly lower UPDRS III score compared to the control group ($P=0.027$).

Further analysis was conducted to compare the magnitude of UPDRS III and PDQ39 score reductions between the two groups. The results revealed that the differences were not statistically significant; please refer to Supplementary Table 1 for detailed information.

Comparison of MMSE and MoCA scores between the groups

As presented in Table 3, there were no significant differences in the MMSE scores between the two groups after the eight-week treatment period ($P=0.038$). The MoCA scores exhibited a substantial increase in the experimental group subsequent to the treatment ($P<0.001$). Additionally, the MoCA scores were markedly higher in the experimental group receiving LCE than in the control group receiving LC ($P<0.001$).

Further analysis revealed that the experimental group displayed significantly greater enhancements in both MMSE ($P=0.004$) and MoCA ($P=0.001$) scores after eight weeks of treatment when compared to the control group. For additional information, please refer to Supplementary Table 1.

Comparison of HAMA and HAMD scores between the groups

As illustrated in Table 4, neither the experimental group nor the control group exhibited statistically significant alterations in their HAMA and HAMD scores ($P > 0.025$). Furthermore, following an 8-week treatment period, no significant differences emerged in either HAMA or HAMD scores between the two groups ($P > 0.025$).

Multivariate analysis of covariance for changes of MoCA scores

We conducted a multivariate analysis of covariance to evaluate the independent impact of "treatment group" on the changes of MoCA scores. In this analysis, the treatment group served as the independent variable, while gender, age, disease duration, and LEDDs were treated as covariates. Our findings indicated that both the "treatment group" factor ($P = 0.001$) and LEDDs ($P = 0.033$) significantly impacted the changes in MoCA scores (ΔMoCA). Please refer to the Supplementary Materials Table 2 for details.

Comparison of changes in HCY and inflammatory cytokines between the groups

As shown in Fig. 1, there were no significant differences in the levels of serum homocysteine (HCY) and inflammatory cytokines, such as TNF-α, IL-6, and IFN-γ between the two groups before treatment. Following an eight-week treatment period, the experimental group exhibited a significant reduction in HCY and IL-6 levels compared to pre-treatment ($P = 0.006$, $P = 0.003$, respectively). Furthermore, the post-treatment IL-6 levels were significantly lower in the experimental group than in the control group ($P = 0.014$). Further analysis revealed that the experimental group had a significantly greater decline in IL-6 after treatment than that of the control group ($P = 0.002$), as presented in Table 5.

Given the disparity in the initial usage of dopamine agonists (DAs) among PD patients across the two groups at baseline, a stratified analysis was performed. This analysis considered the "treatment group" as the independent variable and the change in IL-6 levels (ΔIL-6) as the dependent variable. Additionally, the analysis controlled for LEDDs, the use of DAs, monoamine oxidase type-B inhibitor (MAOBI), and other anti-Parkinson's medications. The findings indicated that the treatment group receiving LCE treatment significantly influenced ΔIL-6 levels, whereas DAs usage had no significant influence on the ΔIL-6 levels. Please refer to Supplementary Table 3 for details.

Linear analysis between ΔMoCA and ΔIL-6 from baseline to final visit

We performed a linear correlation analysis to examine the relationship between the changes in MoCA scores (ΔMoCA) and the changes in IL-6 levels (ΔIL-6). Figure 2 presents the results of the Spearman correlation analysis, which indicated a significant negative correlation between the ΔMoCA and the ΔIL-6 (correlation coefficient: -0.252; $P = 0.024$). To further investigate this relationship, we conducted a multiple linear regression analysis with ΔMoCA as the dependent variable and gender, age, LEDDs, treatment group, and ΔIL-6 as the independent variables. The analysis revealed a significant effect of ΔIL-6 on ΔMoCA (b = -0.170, t = -2.349, $P = 0.021$). Please refer to the Supplementary Materials Table 4 for details.

Discussion

Parkinson's disease is a neurodegenerative disease characterized by the death of dopaminergic neurons, and levodopa remains the gold standard of dopaminergic replacement therapy [24]. When levodopa is metabolized in the body, it follows two main pathways: conversion to dopamine through the dopa decarboxylase (DDC) pathway and conversion to 3-oxygen-methyldopa (3-OMD) via the COMT pathway [25, 26]. Traditional compounded levodopa preparations only inhibit the DDC pathway, which blocks the metabolism of peripheral levodopa to dopamine but lacks inhibition of the COMT pathway [27]. LCE is a compounded dopaminergic agent that inhibits both the DDC and COMT pathways, improving the bioavailability of levodopa and effectively prolonging the "on" period in PD patients, thereby improving motor symptoms [28–30]. Several meta-analysis studies demonstrated that LCE could improve PD patients' motor symptoms and daily living functioning when compared with levodopa/DDCI [28, 29, 31]. In our study, LCE did show improvement in UPDRS III scores in moderate to advanced PD patients, and it was lower than that receiving treatment of LC after the 8-week treatment period. This is consistent with previous findings. However, it is not yet concluded that treated with LCE is superior to LC in terms of the reduction magnitude of the UPDRS III score, although there is a certain trend, which may be explained by the small sample size, and a larger sample size is needed to clarify.

Few studies have reported the efficacy of LCE in improving neuropsychological functions in PD patients. Our study found that the improvement in cognitive function of moderate to advanced PD patients treated with LCE was superior to those treated with LC. This improvement was more obvious in MOCA scores compared to MMSE scores. One possible reason for this result is that the COMT inhibitor can affect cognitive

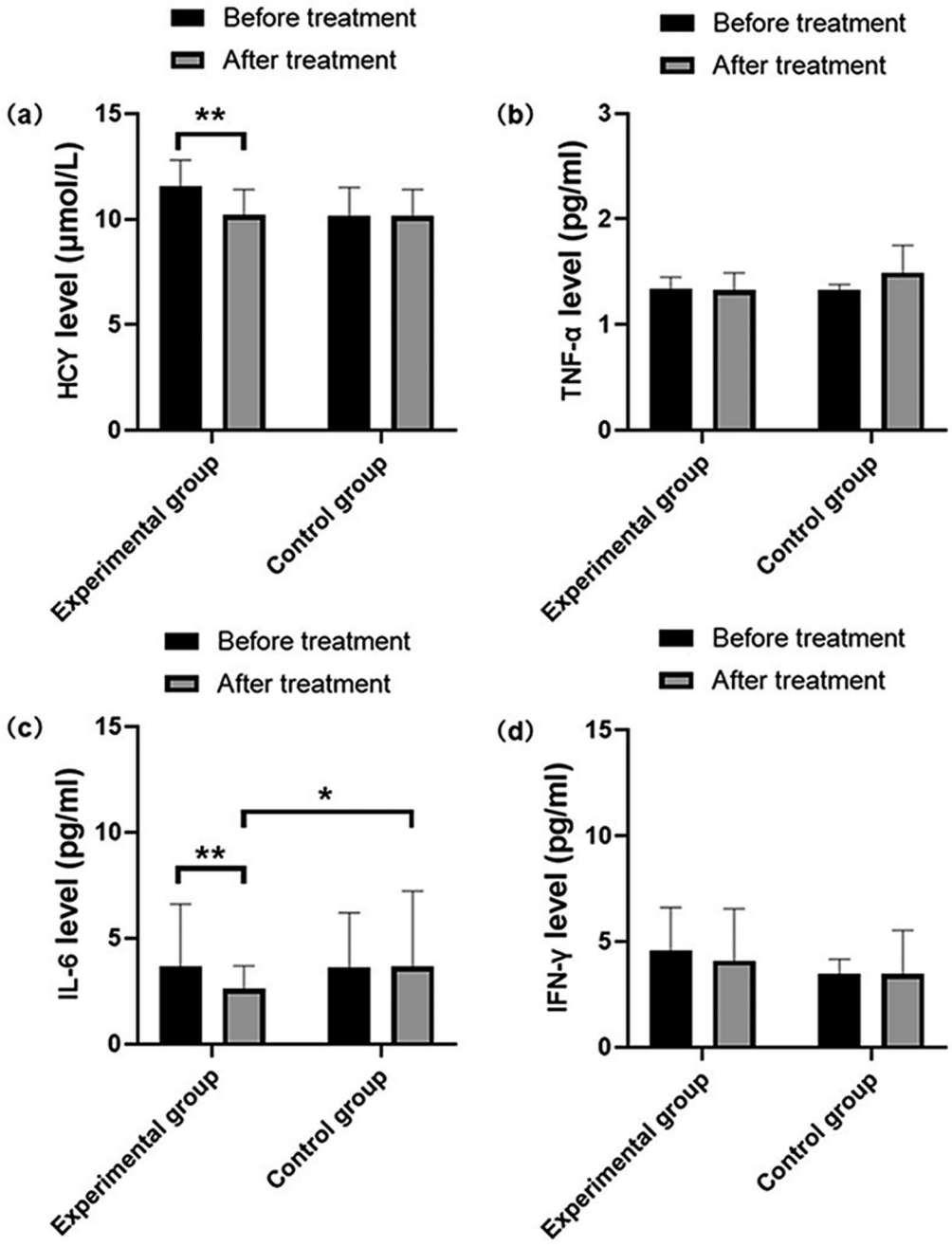

Fig. 1 Comparison of serum HCY (**a**) and inflammatory cytokines (**b**: TNF-α; **c**: IL-6; **d**: IFN-γ) before and after treatment between the groups; An independent samples Mann-Whitney U test was used for between-group comparisons, and a paired Mann-Whitney U test was used for within-group comparisons before and after treatment. * represents p-value less than 0.05, ** represents p-value less than 0.01; HCY, Homocysteine; TNF-α, Tumor necrosis factor-α; IL-6, Interleukin-6; IFN-γ, Interferon-γ; Data was presented as median (IQR)

function by effectively inhibiting the peripheral degradation of catecholamine neurotransmitters such as norepinephrine (NA) and dopamine (DA), thereby increasing the bioavailability of NA and DA, which play a crucial role in cognition maintenance [32, 33]. On the other hand, it is noteworthy that patients treated with LCE had significantly lower serum HCY levels compared to pretreatment, and there was no significant decrease in HCY levels in the control group. Previous studies have highlighted that levodopa is methylated via the COMT pathway after entering the body, leading to the production of methylated S-adenosyl homocysteine (SAH), which is rapidly hydrolyzed and eventually forms HCY [34]. Long-term levodopa monotherapy tends to induce elevated serum HCY levels, while the combination of COMT inhibitors can effectively suppress levodopa-induced

Table 5 Comparison of the difference values between the two treatment groups

	Experimental group ($n=40$)	Control group ($n=40$)	*P*
ΔHCY	-1.10(-3.00, 0.38)	-0.50(-1.55, 1.18)	0.081
ΔTNF-α	-0.06(-0.64, 0.91)	0.04(-0.56, 1.25)	0.627
ΔIL-6	-1.72(-3.81, 0.16)	0.45(-1.02, 2.57)	**0.002**
ΔINF-γ	-0.03(-3.25, 2.75)	-0.37(-1.76, 3.88)	0.754

Δ means post-treatment value minus pre-treatment value.

Data was presented as median (IQR). $p<0.05$ was considered statistically significant.

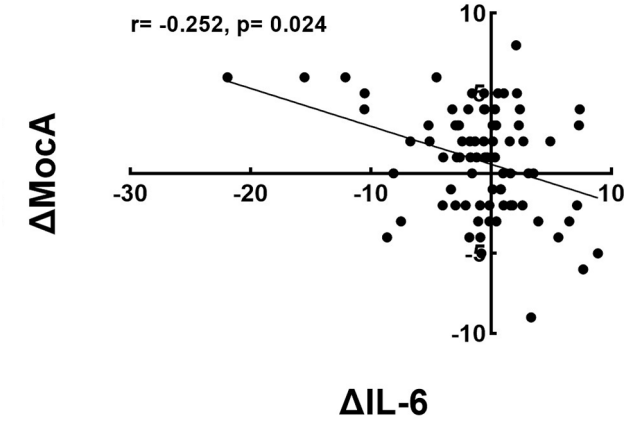

Fig. 2 Correlation between the alteration in MoCA scores (ΔMoCA) and the change in IL-6 levels (ΔIL-6). IL-6, Interleukin-6; MoCA, Montreal Cognitive Assessment

hyperhomocysteinemia [34]. Previous studies have revealed that entacapone can improve the cognitive function of PD patients by reducing potential risk factors that contribute to cognitive decline, such as serum HCY levels [34, 35]. Previous studies have reported that MAO-B inhibitors—rasagiline—can improve certain aspects of cognitive domains in PD patients by increasing the efficiency of dopaminergic transmission [36]. Although our study did not find the effects of other anti-Parkinson's drugs like MAOB inhibitors and dopamine agonists on the improvement of cognitive scores in PD patients, and further research is needed to clarify. And there were no significant improvements in LCE on depression and anxiety scores. However, the potential effects of LCE on these symptoms were not adequately assessed in this study, as patients with major anxiety and major depression were excluded.

The alpha-synuclein deposited in the substantia nigra and striatal regions of PD can promote the production and release of inflammatory cytokines such as TNF-α, IL family, and IFN through activating microglia [8, 37]. Previous studies have demonstrated that the cytokines most closely associated with degenerative damage of substantia nigra and striatum of PD are mainly the IL family, TNF-α, and IFN-γ, and have confirmed that inflammatory cytokine levels in peripheral serum are consistent with those in the central nervous system [38]. A recent meta-analysis showed that the pro-inflammatory cytokine levels such as, IL-6, TNF, and IL-1β, were significantly higher in the peripheral serum of PD patients, indicating that the enhanced peripheral immune inflammatory response is involved in PD origin or progression [11]. The results of this study found that serum post-treatment IL-6 was significantly decreased in PD patients treated with LCE, and its decrease magnitude was significantly greater than that in the control group, suggesting that treatment with LCE helps to downregulate peripheral IL-6 cytokine levels in moderate to advanced PD patients. It has been suggested that levodopa may cause upregulation of pro-inflammatory cytokine levels in PD, while entacapone, a COMT inhibitor, has the effect of enhancing anti-inflammatory activity by downregulating pro-inflammatory cytokines, thus reducing the central dopaminergic neurons damage caused by peripheral inflammatory responses [14].

Linear correlation analysis revealed that there was a significant negative correlation between the improvement of MoCA scores and the reduction of IL-6 levels. Further multivariate linear analysis revealed that both treatment of LCE and IL-6 reduction had independent significant impact on the improvement of MoCA scores after the 8-week treatment period. The possible reason for this result is that IL-6 signaling promotes brain repair by facilitating the neuroprotective effect of promoting PD microglia regeneration and cognitive function recovery [39]. This finding is consistent with a recent study that demonstrated significantly higher cytokine levels in PD patients with cognitive dysfunction compared to those without cognitive dysfunction, and the severity of cognitive dysfunction was significantly negatively correlated with cytokine levels such as IL-6 and TNF-α in plasma extracellular vesicles [40]. Based on the findings above, we hypothesized that LCE might improve the cognitive function of moderate to advanced PD patients through downregulating the levels of inflammatory cytokines like IL-6.

A major limitation of the study is the small sample size and short observation period due to the impact of the three-year epidemic of COVID-19 and financial constraints, so we cannot assert the reliability of negative results for certain outcome measures that did not exhibit differences. Secondly, this study is unblinded, but we set the clinical assessors who were blinded to the participants' medication or dosing information and the results of blood test indicators to perform all the clinical assessments in order to minimize the potential bias. Thirdly, most of the included PD patients were in the Hoehn-Yahr stage 3–4; due to this defect, it is difficult to generalize this conclusion to PD patients in Hoehn-Yahr stage

5. Fourthly, the study was a monocentric, small sample, open-label randomized controlled trial, and in the future, it is necessary to further expand the sample size and perform a large double-blind multi-center randomized controlled trial study to verify our conclusions. Nevertheless, we remain hopeful that our findings will contribute meaningfully to clinical treatment.

Conclusion

Based on the above research, we found that LCE can help improve motor symptoms and quality of life in moderate to advanced PD patients. In addition, LCE may improve cognitive function, as well as downregulate the serum cytokine IL-6 levels in moderate to advanced PD patients, which is superior to LC. On account of a significant negative correlation between the improvement of MoCA scores and the reduction of IL-6 levels, we hypothesize that LCE may improve the cognitive function of moderate to advanced PD patients through suppressing the levels of inflammatory cytokines like IL-6.

Abbreviations

PD	Parkinson's disease
LCE	Levodopa/Carbidopa/Entacapone
LC	Levodopa/Carbidopa
UPDRS III	Unified Parkinson's Disease Rating Scale part III
PDQ-39	Parkinson's Disease Questionnaire-39
MMSE	Mini-Mental State Examination
MoCA	Montreal cognitive assessment
HAMA	Hamilton Anxiety Scale
HAMD	Hamilton Depression Scale
COMT	Catechol O-methyltransferase
HCY	Homocysteine
TNF-α	Tumor necrosis factor-α
IL-6	Interleukin-6
IFN-γ	Interleukin-γ
LEDDs	Levodopa-equivalent daily doses
H-Y	Hoehn-Yahr

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12883-025-04128-1.

Supplementary Material

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Author contributions

D-J. X. designed the study, acquired funding and edited the manuscript; Y.F. and H-F.L. did the statistical analysis; Y.F. prepared the original draft; Y-L.S. and M-M.H. did the clinical assessment; D-J.X. and J-P.H. did the outcomes assessment, supervision and project administration; All authors contributed to the acquisition and interpretation of data and revised the manuscript for intellectual content. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets and supplementary information in this manuscript are available from the first or corresponding author on reasonable request. An unauthorized version of the Chinese MMSE was used by the study team without permission, however this has now been rectified with PAR. The MMSE is a copyrighted instrument and may not be used or reproduced in whole or in part, in any form or language, or by any means without written permission of PAR (http://www.parinc.com).

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of the Dongyang People's Hospital, Affiliated to Wenzhou Medical University (Ethic ID: 2021-YX-037). All participants signed written informed consents. All methods were performed in accordance with the national guidelines and regulations and the ethical standards of the Declaration of Helsinki 1964.

Consent for publication

Not Applicable.

Competing interests

The authors declare no competing interests.

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