



THE ROLE OF INFLAMMATION IN EARLY AND LATE PHASE OF PARKINSON DISEASE

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ARTICLE INFO

Received:

07 Dec 2020

Received in revised form:

08 Feb 2021

Accepted:

16 Feb 2021

Available online:

28 Feb 2021

Keywords: Role, Inflammation, Early, Late, Parkinson, Disease

ABSTRACT

This study aimed at exploring the role of inflammation in different stages of PD in a sample of PD patients in Al Madinah city, Saudi Arabia, and to identify the relationship between disease duration and level of the inflammatory markers. 22 Parkinson disease (PD) patients in Al Madinah City were subjected to a cross-sectional analysis. Motor and non-motor symptoms evaluation was carried out using the Unified Parkinson's Society Movement Disorders Rating Scale (NMSS) and the Hoehn and Yahr stages. Serum samples and C-reactive protein (CRP), erythrocytes (ESR), and IL-1 levels were measured, were taken.

The mean level of CPR was significantly positive concerning the length of the PD, (NMSS), Hoehn-Yahr, and ESR, and important concerning Hoehn and Yahr. The average ESR level for participants was substantially positively correlated, with both the NMSS and the average IL-1 levels, although there was a substantial negative correlation between the average level IL-1 and the mean level Unified Parkinson's (UPDRS). This study recommended future studies done on larger samples that include comprehensive and combined biomarkers for effective PD diagnosis and treatment.

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To Cite This Article: Mohammed Mosaad, Abeer Furayj Aljahdali, (2021), "The Role of Inflammation in Early and Late Phase of Parkinson Disease", *Pharmacophore*, 11(1), 51-56.

Introduction

In Saudi Arabia, Parkinson's disease (PD) is the most common movement disorder. [1]. Post-Alzheimer neurodegenerative disease is the second most common. PD showed damage by alpha-synuclein comprising inclusion bodies (Lewy pathology resulting in a typical motor impairment) to significant nigra (SN) neurons of the substantial neurons. [2] It was calculated that PD was 1–3 percent in the population aged 65 years and older. [3] Patients with PD experience non-engine symptoms, including cognitive impairments, in addition to motor symptoms [4], depression [5], and gastrointestinal dysfunction. [6]

A lot of recent studies show that different component of brain immune system has an important role in neuroinflammation events and PD pathogenesis [7], and the patients affected have reported high inflammation mediators' level in the cerebrospinal fluid and brain. [8-11]

Few studies focused on the concentrations of inflammatory markers in PD. In terms of clinical trials with anti-inflammatory agents, it might be an important issue to know whether an elevated level of inflammatory markers can have correlated with more symptoms regarding motor and non-motor impairment in PD. [12]

The current study, therefore, aimed to answer and identify if there is a relation between the level of inflammatory markers and if these markers can contribute to disease course in motor symptoms comparing to non-motor symptoms in PD. In the Kingdom of Saudi Arabia (KSA), there were no studies done to determine the relationship between the level of inflammatory markers and disease in PD. That is why this study was done to explore the level of inflammatory markers related to disease course, and the motor or non-motor symptoms presence, as this approach can help in better identification of the inflammation's role in these symptoms. The study aimed at exploring the inflammation's role in different stages of PD in a sample of PD patients in Al Madinah city, Saudi Arabia, and to identify the relationship between disease duration and level of the inflammatory markers.

Materials and Methods

Design of the study

The present study type was an observational cross-sectional.

Setting and duration

The study was conducted in the Neurology Outpatient Clinics in King Fahad Hospital in Al Madinah Al Munawwarah City, Saudi Arabia during the period from December 2018 to May 2019.

Sampling methodology

The minimum sample size required was 22 participants who were determined by using the open Epi sample size calculator online at a 95% confidence interval and with a proportion of 30% that were used as inputs.

The inclusion and exclusion criteria

They were: (1) patients who had been diagnosed by neurologist based on NINDS Diagnostic Criteria for PD, (2) patients had disease duration 6 years or less, and (3) patients or caregivers should be able to understand either the Arabic or English language. (1) patients taking any medication that may change inflammatory marker levels, like anti-inflammatory or immunosuppressive medications, (2) patients with diabetes mellitus have been diagnosed, (3) patients with extreme cognitive impairment that may interfere with the involvement of the research, and (4) patients with chronic inflammatory disorders have been omitted.

Study instrument

Using the Single Parkinson's Disease Scale Movement Disorders Society, demographic data have been gathered through a pre-designed survey and motor signs examination. Using the Non-Motor Symptoms Scale, the Non-Motor Symptom Scale (NMSS) evaluation was carried out to determine the overall non-motor symptoms. During the Hoehn and Yahr phases, motor symptoms were assessed. According to the PPMI Protocol, the level of inflammatory markers has been determined by the collection of serum. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) and IL-1 were analyzed in the serum samples. Measures were rigorously analyzed according to the instructions of the manufacturer.

Statistical analysis

An analysis of data has been carried out using version 20 of the Social Sciences Statistical Package (SPSS). The quality data were expressed as numbers and percentages, and the mean and standard deviation (mean \pm SD) of quantitative data was expressed. The Mann-Whitney (U-Test) and Kruskal-Wallis experiments were carried out to determine the relationship of independent non-parametric quantitative variables. Statistically important was a p-value <0.05 .

Results and Discussion

Among the 22 participants, 54.55 were females, 86.4% had a dose of 125 mg of their treatment. the mean age of the participants was (59.54 \pm 15.75) years, and the mean duration of PD was (3.63 \pm 1.96) years. According to the participants' clinical data, the mean score of the Unified Parkinson's Disease Rating Scale (UPDRS) was (65.13 \pm 30.06), and the mean score of NMSS was (7.86 \pm 5.64). As regards the inflammatory markers, the mean levels of CPR, ESR, and IL-1 were (7.7 \pm 5.71, 24.68 \pm 14.19, and 18.3 \pm 8.28) respectively. According to the participants' Hoehn and Yahr stages; 27.3%, 22.7%, 18.2% and 13.6% had stage 1, 2, 3, 4, and 5 respectively (**Table 1**).

(**Table 2**) shows that the mean CPR level of the participants had a significant positive correlation with PD duration, Nonmotor Symptoms Son cale (NMSS) score, Hoehn-Yahr stage, and the mean ESR level ($p < 0.05$). On the other hand, The CPR level was linked to the participant's age, to the UPDRS (Unified Parkinson's Disease Rating Scale), and a mean IL-1 ($p > 0.05$) level of the CPR level.

Between participants' mean CPR levels and their Hoehn and Yahr stage, a significant correlation between, as patients in stage 5 had a significantly higher CRP level than others ($p < 0.05$). The mean CPR level with the participants and dosage of their therapy was not significantly linked (**Table 3**).

The mean ESR level of the participants and both the Non-Motor Symptoms Scale (NMSS) and the IL-1 ($p < 0.05$) mean were significantly associated positively. At the same time, the mean ESR level and the participant age, length of the PD, and settlement of the Unified Parkinson's Disease Scale (UPDRS) and the Hoehn-Yahr stage ($p > .05$) are not significantly positively associated (**Table 4**).

(**Table 5**) shows that the mean ESR level, the sex of patients, their Hoehn and Yahr stage, and the dose of treatment were not important.

(**Table 6**) indicates that the mean negative association between the mean levels of IL-1 and the average rating scale of Unified Parkinson (UPDRS) was observed ($p < 0.05$). On the contrary, the mean IL-1 level was non-significantly adverse to that of the participants' age, PD period, and the mean Nonmotor Symptoms Scale (NMSS) score ($p > 0.05$), while a non-significant positive correlation was found between the mean IL-1 level and the mean Hoehn-Yahr stage ($p > 0.05$).

In (Table 7), the relationship between the level of IL-1 and gender, their Hoehn and Yahr stage, and their treatment dose is significant and not significant.

Table 1. Demographic and clinical data overview of studied participants

Variable	No. (%)
Gender	
- Female	12 (54.5)
- Male	10 (45.5)
Hoehn and Yahr stage	
- Stage 1	6 (27.3)
- 2	5 (22.7)
- 3	4 (18.2)
- 4	3 (13.6)
- 5	4 (18.2)
Dose	
- 125 mg	19 (86.4)
- 1 gm	3 (13.6)
Variable	(Mean ± SD)
Age (Mean ± SD) years	59.54 ± 15.75
PD duration (Mean ± SD) years	3.63 ± 1.96
Unified rating scale (UPDRS) for Parkinson's Disease Rating (Mean ± SD)	(65.13 ± 30.06)
Nonmotor Symptoms Scale (NMSS) score (Mean ± SD)	7.86 ± 5.64
CRP (Mean ± SD)	7.7 ± 5.71
ESR (Mean ± SD)	24.68 ± 14.19
IL-1 (Mean ± SD)	18.3 ± 8.28

Table 2. Spearman correlation between CRP level, and age, PD duration, UPDRS score, NMSS score, Hoehn-Yahr stage, ESR and IL-1 levels

Variable	CRP level	
	R	p-value
Age (Mean ± SD) years	0.2	0.35
PD duration (Mean ± SD) years	0.55	0.007
Unified rating scale (UPDRS) for Parkinson's Disease (Mean ± SD)	0.32	0.14
Nonmotor Symptoms Scale (NMSS) score (Mean ± SD)	0.57	0.005
Hoehn-Yahr stage (Mean ± SD)	0.56	0.007
ESR (Mean ± SD)	0.49	0.01
IL-1 (Mean ± SD)	0.15	0.49

Table 3. Relationship between CRP level and patients' gender, their Hoehn and Yahr stage, and the dose of treatment taken

Variable	CRP	Test	p-value
Gender			
- Female	6.42 ± 5.45	1.28*	0.2
- Male	9.24 ± 5.9		
Hoehn and Yahr stage			
- Stage 1	3.86 ± 4.92	7.92**	0.09
- 2	7.87 ± 6.15		
- 3	7.09 ± 2.94		
- 4	8.04 ± 8.07		
- 5	13.61 ± 2.92		
Dose			
- 125 mg	8.4 ± 5.79	1.29*	0.22
- 1 gm	3.28 ± 2.51		

N.B.: *Mann-Whitney (U) Test

** Kruskal-Wallis test

Table 4. Spearman correlation between ESR level, and age, PD duration, UPDRS score, NMSS score, Hoehn-Yahr stage, CRP and IL-1 levels

Variable	ESR level	
	R	p-value
Age (Mean ± SD) years	0.27	0.22
PD duration (Mean ± SD) years	0.3	0.17
Unified rating scale (UPDRS) for Parkinson's Disease (Mean ± SD)	0.07	0.75
Nonmotor Symptoms Scale (NMSS) score (Mean ± SD)	0.56	0.006
Hoehn-Yahr stage (Mean ± SD)	0.19	0.38
IL-1 (Mean ± SD)	0.46	0.02

Table 5. Relationship between ESR level and patients' gender, their Hoehn and Yahr stage, and the dose of treatment taken

Variable	ESR	Test	p-value
Gender			
- Female	22.66± 14.95	0.32*	0.34
- Male	27.1± 13.58		
Hoehn and Yahr stage			
- Stage 1	23.33 ±18.16	1.38**	0.84
- 2	22.4 ±17.57		
- 3	31.25± 13.32		
- 4	22.33 ±12.85		
- 5	24.75 ±9.21		
Dose			
- 125 mg	24.73 ±13.71	0.48*	0.65
- 1 gm	24.33 ±20.5		

N.B.: *Mann-Whitney (U) Test

** Kruskal-Wallis test

Table 6. Spearman correlation between IL-1 level, and age, PD duration, UPDRS score, NMSS score, Hoehn-Yahr stage, CRP and ESR levels

Variable	IL-1 level	
	R	p-value
Age (Mean ± SD) years	-0.17	0.42
PD duration (Mean ± SD) years	-0.19	0.39
Unified rating scale (UPDRS) for Parkinson's Disease Rating (Mean ± SD)	-0.37	0.08
Nonmotor Symptoms Scale (NMSS) score (Mean ± SD)	-0.05	0.81
Hoehn-Yahr stage (Mean ± SD)	0.03	0.86

Table 7. Relationship between IL-1 level and patients' gender, their Hoehn and Yahr stage, and the dose of treatment taken

Variable	IL-1	Test	p-value
Gender			
- Female	16.39± 7.45	0.56*	0.58
- Male	20.59± 9.03		
Hoehn and Yahr stage			
- Stage 1	18.9 ±9.12	1.64**	0.8
- 2	13.48± 6.59		
- 3	18.42± 8.15		
- 4	21.45 ±10.98		
- 5	20.95 ±8.83		
Dose			
- 125 mg	18 ±8.23	0.43*	0.71
- 1 gm	20.23 10.23		

N.B.: *Mann-Whitney (U) Test

** Kruskal-Wallis test

This study investigated whether there was any relationship between the level of inflammatory markers and PD course, and the role of inflammation in motor or non-motor symptoms.

The study found that the CRP and ESR, IL-1B levels, which are considered good indicators of systemic inflammation may have a predictive value for Parkinson's disease. Also, the study revealed another important finding that is the presence of a statistically significant positive correlation between the CPR level of the participants with PD duration, Nonmotor Symptoms Son scale (NMSS) score, Hoehn-Yahr stage, and the mean ESR level ($p < 0.05$). At the same time, ESR was found to have a significant positive correlation with both Nonmotor Symptoms Scale (NMSS) scores and the mean IL-1 level ($p < 0.05$).

IL-1b which is another indicator of inflammation was found to have no significant relationship either with mean PD duration of motor and non-motor symptoms.

Recent studies had reported that PD was associated with systemic inflammation, where the CRP and ESR levels were found to be high in 51 Parkinson's patients studied. [12, 13] Another study has found that IL-1b also was high in 58 patients. [12] IL-1b is a pro-inflammatory cytokine with the pleiotropic brain and peripheral biologic involvement. This cytokine is one of the principal causes of PD neurodegeneration by inflammation. [14]

In the present work, it was found that there was a relationship between the PD duration, non-motor symptoms, and HY stages with CRP level and a significant positive relationship were found between ESR levels and nonmotor symptoms, which are consistent with the previous study [14], however, the researcher did not detect any association or significant positive relationship between IL-1b values and PD duration or motor - non-motor symptoms.

As a difference from Kim et al., study, the researcher compared the IL-1b values with drug-using and disease duration, but a non-significant negative correlation was found between the mean IL-1 level and the PD duration. A non-significant relationship was found between the IL-1 level and the dose of the patients' treatment. [12]

CRP which is produced by the liver and the adipose tissue is commonly used in clinical practice as an acute or chronic inflammation biomarker. The relationship between the CRP and the PD was investigated in previous studies [12, 15], which reported that the CRP levels were higher in PD patients than the healthy groups. Also, they reported that levodopa + carbidopa combinations were found to increase the CRP levels in PD. [16]

Another research found that in PD patients, CRP levels were higher. [17] In a second study, the CRP levels were higher in the PD community and higher CRP levels showed a positive association with the period of this disease and with the stages of Hoehn Yahr. [18]

An important correlation between the participant mean CPR level and their Hoehn and Yahr stage was observed during this study, as patients at stage 5 had a significantly higher level of CRP relative to other stage levels ($p < 0.05$). Moreover, the mean CPR level and the dosage of your levodopa treatment are insignificant. These findings are in accordance with other studies that did not identify any correlation between CRP levels and levodopa dosage. [18, 19]

In the other polytherapy groups, the researcher could not make correlation analyses because there were not enough patients for powerful statistical analyses.

A retrospective study has revealed that the CRP levels were independent of the disease duration and the incidence of disease-related mortality. [16]

ESR is a hematological test to detect inflammation unspecified and can be identified as the sediment of Red Blood Cells (RBCs) within 1 hour. [20]

The relationship between the ESR and the PD was investigated in a previous study, and it reported that ESR level was high in 51 PD patients [13], and there was a strong positive association between the participant's average levels of the ESR and both the Non-motor Scale of Symptoms (NMSS). Also, the mean ESR, and the participant age, PD duration, Unified Parkinson's Rating Scale (UPDRS) score, Hoehn-Yahr level, were not significantly positively correlated.

Conclusion

The present study was done on 22 patients and revealed that that the mean CPR level of the participants had a significant positive correlation with PD duration, Nonmotor Symptoms Son scale (NMSS) score, Hoehn-Yahr stage, and the mean ESR level. At the same time, the CRP was substantially higher in patients with Hoehn and Yahr stage 5 than in other stage cases. A strong positive correlation with the participants' mean ESR level and both NOSS scales and the mean IL-1 level has been found and an important negative correlation between median IL-1 and mean Unified Parkinson's Disease Rating Scale (UPDRS) was reported. A positive correlation was found between the average IL-1 level. The report proposed future research on broader samples with systematic, combined biomarkers to diagnose and treat PD effectively. These studies may provide new ways of treating diseases, especially in the early stages.

Limitations

The limited sample size selected and analyzed from a hospital setting was a limitation of this work.

Acknowledgments: The author/s would like to extend his/her/their deepest gratitude to all people who helped in many ways, whether small or big means, in finishing this research work.

Conflict of interest: None

Financial support: Self-funded study.

Ethics statement: The Ethics Committee for Health Studies in Al-Madinah gave written consents to all students and ethical approval for the study.

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