Cellular and Molecular Biology
E-ISSN : 1165-158X / P-ISSN : 0145-5680
www.cellmolbiol.org

Correlation between the peripheral neuropathy and levels of hs-CRP, IL-1β and IL-6 in senile Parkinson's disease patients

Yongzhi Zhang[1#], Yihan Liu[2#], Yanmin Li[2], Sai Zhang[2], Xiaoyang Yuan[2], Chenfei Liu[2], Lijuan Geng[2], Ping Gu[2*]

[1] Department of Neurology, The First Hospital of Hebei Medical University, Shijiazhuang, Hebei 050000, China; Graduate School of Hebei Medical University, Shijiazhuang, Hebei050032, China
[2] Department of Neurology, The First Hospital of Hebei Medical University, Shijiazhuang, Hebei 050000, China

#They contributed equally to this work

ARTICLE INFO

Original paper

Article history:
Received: January 19, 2023
Accepted: March 31, 2023
Published: April 30, 2023

Keywords:

hs-CRP, IL-1β, IL-6, Parkinson's disease, peripheral neuropathy

ABSTRACT

This study was carried out to investigate the correlation between the onset of peripheral neuropathy and levels of hypersensitive C-reactive protein (hs-CRP), interleukin 1β (IL-1β) and IL-6 in senile Parkinson's disease (PD) patients. For this purpose, a total of 60 PD patients and 60 age-matched healthy subjects were enrolled in this study and received the assessment for peripheral nerves by using the quantified method. Besides, levels of hs-CRP, IL-1β and IL-6 in serum were determined to analyze the correlation between the clinical features, including the severity of PD and cognitive decline, and the levels of hs-CRP, IL-1β and IL-6. Results showed that PD patients had more cases of peripheral neuropathy than those in the healthy control group. Levels of hs-CRP, IL-1β and IL-6 in the serum of PD patients were much higher than those in the healthy control ($P<0.05$). Besides, PD patients had lower scores of MMSE and MoCA but higher CNPI scores when compared to the healthy control group. As a result, we found that the severity of peripheral neuropathy was in a positive correlation with the levels of hs-CRP, IL-1β and IL-6. It was concluded that PD patients generally have peripheral neuropathy that may correlate with the increases in the levels of hs-CRP, IL-1β and IL-6, and early intervention may mitigate the development and progression of peripheral neuropathy.

Doi: http://dx.doi.org/10.14715/cmb/2023.69.4.19
Copyright: © 2023 by the C.M.B. Association. All rights reserved.

Introduction

Parkinson's disease (PD), as a kind of neurodegenerative disease, have the hallmarks of abnormal accumulation of α-synuclein and loss of dopaminergic neurons, leading to a variety of clinical features, including the myotonia, bradykinesia, tremor and postural instability (1-3). Pathogens of PD include autonomous antibodies in the nerve, a reduction in the number of lymphocytes in peripheral blood, a decline in the secretion of immunoglobin and variations in the cytokines secreted by cells in the brain and peripheral blood (4).

Neuroinflammation is a key process of PD. IL-1β can induce the inflammatory cascade by glutamate excitotoxicity to result in the death of neurons, and the level of IL-1β fluctuates dynamically in the progression of PD (5-7). In addition, IL-1β is involved in levodopa-induced dyskinesia (8,9), leading to the decline in cognitive function and the inhibition of hippocampus-dependent learning ability (10). Interleukin 6 (IL-6) plays a pivotal role in the pathogenesis of inflammatory diseases and in sustaining the physiological homeostasis in nerves. Severe neuropathological changes, including multiple sclerosis (MS), PD and Alzheimer's disease, are related to the changes in the levels of IL-6 in the brain (11,12). C-reactive protein, as a common acute phase protein, is generated mainly by the liver in inflammation and IL-6-induced responses. Recently, hs-CRP performs much better in determining subclinical inflammation than CRP (13). An increase in the level of hs-CRP is also noted in a variety of neurodegenerative diseases and neurovascular diseases, including PD and age-related macular degeneration (14,15). Though people have gained a sufficient understanding of the role of inflammation in neurodegenerative changes, potential inflammatory pathogenesis and the correlation with PD-specific symptoms remain unknown. Currently, there remains no evidence suggesting that inflammation is commonly shared by all neurodegenerative diseases. In this study, we aimed to investigate the correlation between PD-specific inflammatory markers and clinical symptoms, providing valuable information for elucidating the pathogenesis of PD to improve the diagnosis and prognosis of PD.

Materials and Methods

PD group and control group

PD group: 60 PD patients who were treated in The First Hospital of Hebei Medical University between March 2021 and September 2022 were enrolled into the PD group as per the following criteria: Patients with the symptoms conforming to diagnostic criteria of PD stipulated by Motor Dysfunction and Parkinson's disease Group, Neuro-

* Corresponding author. Email: yuzhoushengyuan@126.com

logy Society of Chinese Medical Academy (16); Patients that were proficient in language and expression and could cooperate with the arrangement of staff; Patients who or whose family were informed of the study and signed the written informed consent.

Control group: 60 healthy subjects were selected randomly from the people who visited the physical examination center of The First Hospital of Hebei Medical University during the same period and enrolled into the control group.

A comparison of the baseline data between the two groups showed no evident difference (P>0.05), suggesting that the data were comparable.

Assessment of peripheral nerve injury

At room temperature (25°C), all 120 subjects fulfilled the determination of sensory and motor nerve conduction velocity (SCV, MCV). For those with abnormal measurements, the determination was repeated and the measurement that could reflect better neurological function would be taken. Criteria for assessment of peripheral nerve injury: With a critical value (Critical value = Average of nerve conduction velocity in normal adults – 2.5 × standard deviation), subjects with measurement lower than critical value would be considered as significant asymmetry around the nerve (> 10% of conduction velocity), or latency of F wave > 130% of the upper bound of normal range and extraction rate < 70%, were considered as an anomaly.

Measurement of hs-CRP, IL-1β and IL-6 in serum

In the morning, 3 mL of fasting venous blood was drawn from subjects in two groups and placed in a 100 μL tube supplemented with 2% ethylene diamine tetraacetic acid (EDTA). Tubes were then centrifuged at 3000 r/min for 10 min to obtain the supernatant which was then stored at -80°C for the following determination. Enzyme-linked immunosorbent assay was performed to determine the levels of IL-1β and IL-6, while hs-CRP was measured by turbidimetry.

Evaluation of cognitive function

Cognitive function was evaluated by using the Minimum Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA) and Chinese version of the neuropsychiatric inventory (CNPI). Patients with higher scores of MMSE and MoCA would be considered to have a better cognitive function, while the cognitive function of those with higher CNPI scores would be poor.

Statistical analysis

SPSS 19.0 software was utilized to perform the statistical analysis. Measurement data were expressed in form of mean ± standard deviation (SD), and t-test would be carried out to determine the difference between two independent samples. Enumeration data were compared by chi-square test, while correlation would be validated by Spearman correlation analysis.

Results

Prevalence of peripheral neurology of patients in two groups

There were 25 patients (41.7%) with peripheral neuropathy in the PD group, significantly more than 13 (21.7%) in the healthy control group (P<0.05).

Comparison of the UA, hs-CRP, IL-1β and IL-6 between two groups

UA level of patients in the PD group was much lower than that in the healthy control group (P<0.01), while levels of hs-CRP, IL-1β and IL-6 in the serum of patients in PD group were much higher than those in the healthy control group (P<0.01, Table 1 and Figure 1).

Comparison of the cognitive function between two groups

In comparison with the healthy control group, patients in the PD group had lower MMSE and MoCA scores but higher CNPI scores (P<0.05, Table 2 and Figure 2).

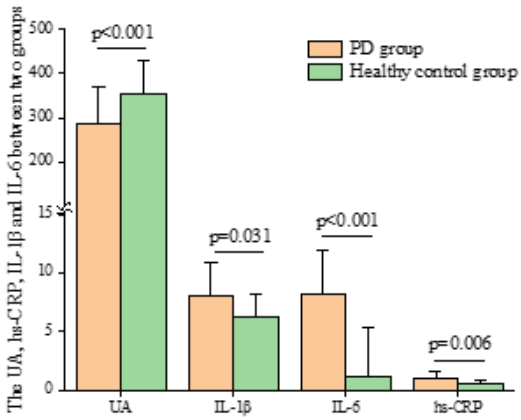

Figure 1. Comparison of the UA, hs-CRP, IL-1β and IL-6 between PD and healthy control groups.

Table 1. Comparison of the UA, hs-CRP, IL-1β and IL-6 between two groups (mean ± SD).

Group	UA (μmol /L)	IL-1β (pg /ml)	IL-6 (pg /ml)	hs-CRP (mg/L)
PD	285.35±82.64	7.96±2.82	8.16±3.72	0.93±0.64
Healthy control	353.82±76.05	6.24±1.85	1.20±4.06	0.50±0.30
t	5.390	2.725	11.862	3.305
P	0.000	0.031	0.000	0.006

Table 2. Comparison of the cognitive function between two groups (mean ± SD).

Group	n	MMSE score	MoCA score	CNPI score
PD	60	18.35±2.45	23.85±3.07	19.36±2.46
Healthy control	60	23.56±3.28	29.65±2.85	15.20±1.85
t		6.465	6.364	7.268
P		0.000	0.000	0.000

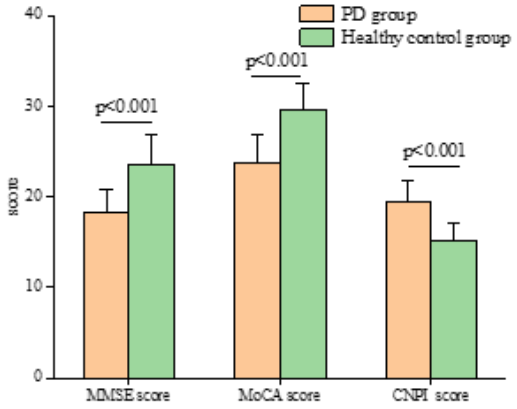

Figure 2. Comparison of the cognitive function between PD and healthy control groups.

Comparison of the sensory and motor nerve conduction velocity between two groups

In the PD group, patients with peripheral neuropathy had a lower conduction velocity in tibial and sural nerves as compared to those in the healthy control group (P<0.05), while similar changes were also seen in a comparison of those with no peripheral neuropathy between two groups (P<0.05, Table 3 and Figure3).

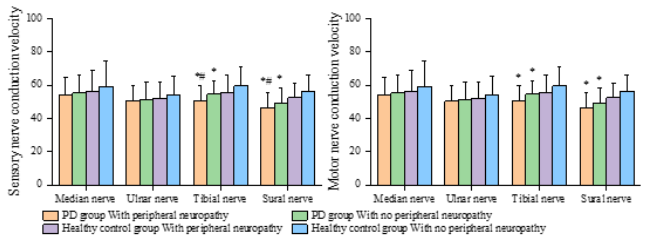

Figure 3. Comparison of the sensory and motor nerve conduction velocity between two groups. Note: * P<0.05 *vs.* the subjects with no peripheral neuropathy in healthy control group; # P<0.05 *vs.* the subjects with peripheral neuropathy in healthy control group.

Analysis of correlation between peripheral nerve injury and levels of hs-CRP, IL-1β and IL-6 in serum

According to the analysis of the Pearson correlation coefficient, we found that levels of hs-CRP, IL-1β and IL-6 were in negative correlation with the sensory and motor nerve conduction velocity, but in positive correlation with the latency of sensory and motor nerve conduction (all P<0.05; Table 4).

Discussion

Generally, PD patients usually suffer the evident injury of peripheral neurological function, and as the disease progresses, they will be afflicted by sensory or motor dysfunction, including static tremor and postural instability – the more severe the peripheral nerve injury is, the poorer the patients behave in balance. Thus, understanding the correlation between the pathogenesis of peripheral neuropathy and disease-related factors is critical to the prevention and treatment of PD.

IL-1β, as an effective pro-inflammatory cytokine, can target a variety of cells by interacting with the IL-1 receptor, including neurons and microglial cells (17). IL-1 can maintain the lipopolysaccharide-induced inflammatory cycle by upregulating the NF-κB-mediated pro-inflammatory cytokines. Besides, IL-1β is up-regulated in the cerebrospinal fluid (CSF) (18), corpus striatum (19) and SN (20) in PD patients. Genetic studies have shown that the T allele in the regulation area of *IL-1β* in PD patients is up-regulated, increasing IL-1β (21,22). In our study, we infer that the overexpression of IL-1β in patients may result in the increase of susceptibility of dopaminergic neurons to the exogenous toxins, with an increase in the risk of PD development. The data above suggested that IL-1β may have a key role in the development of PD, which, however, has been reported in published studies (23-25). Similarly, we also found that the level of IL-1β in the serum of PD patients elevated significantly as compared to the healthy control group.

IL-6, as an effective factor inducing the acute response

Table 3. Comparison of the sensory and motor nerve conduction velocity between two groups (mean ± SD, m/s).

Group	n	Sensory nerve conduction velocity				Motor nerve conduction velocity			
		Median nerve	Ulnar nerve	Tibial nerve	Sural nerve	Median nerve	Ulnar nerve	Tibial nerve	Sural nerve
PD									
With peripheral neuropathy	25	49.2±8.1	48.9±7.9	36.2±3.5*#	44.7±4.5*#	54.1±10.3	50.4±9.2	50.2±9.6*	46.6±8.7*
With no peripheral neuropathy	35	50.2±8.3	49.0±8.3	39.5±5.0*	49.6±9.5*	55.2±11.2	51.2±10.3	54.6±8.1*	49.2±9.1*
Healthy control									
With peripheral neuropathy	13	53.2±9.2	52.0±8.6	42.1±4.0	52.2±8.6	56.2±12.4	52.0±10.1	55.8±10.3	52.5±8.5
With no peripheral neuropathy	47	55.4±10.6	56.0±11.5	44.3±8.3	56.4±13.2	59.2±15.5	53.8±11.4	59.6±11.3	56.2±10.2

Note: * P<0.05 *vs.* the subjects with no peripheral neuropathy in the healthy control group; # P<0.05 *vs.* the subjects with peripheral neuropathy in the healthy control group.

Table 4. Analysis of correlation between peripheral nerve injury and levels of hs-CRP, IL-1β and IL-6 in serum.

Indicators	Motor nerve conduction velocity	Latency	Sensory nerve conduction velocity	Latency
	r	r	r	r
IL-1β	-0.712	0.721	-0.781	0.689
IL-6	0.622	-0.726	0.650	-0.652
hs-CRP	0.664	-0.653	0.693	-0.603

of the liver (26), is involved in the differentiation of lymphocytes and monocytes and targets the B lymphocyte, T lymphocyte, hepatocyte and hemopoietic progenitor cell (27). In addition, IL-6 is pivotal to the dynamic balance of neurons, and the lack of IL-6 can induce a reduction in the activation of glial cells and alterations in cognitive function in traumatic brain injury (28,29). Other, excessive generation of IL-6 in the brain can also induce nerve degenerative changes (30,31). Likewise, our studies have shown that in the PD group, the IL-6 level in patients was much higher than that of the healthy control group, and, PD patients performed poorly in MMSE and MoCA scores, with a higher score of CNPI.

Hs-CRP is a non-specific marker of low-grade inflammation. Though hs-CRP may have a role in the acute phase of infection or organic injury, hs-CRP level in circulation can reflect ongoing low-grade inflammation (32). Neuroinflammation or stimuli can trigger the generation of peripheral inflammatory proteins and increase cell permeability, and the increased inflammatory proteins in CNS can further augment the level of peripheral inflammatory proteins by passing through the blood-brain barrier (33). In this case, the peripheral concentration of inflammatory protein can display the changes in the neuroinflammation of CNS. Previous literatures have shown that hs-CRP is increased in PD patients (34-36). Consistent with these studies, we also noted the increases in hs-CRP in PD patients when compared to the healthy control group.

This study, however, is limited in the following aspects: small sample size, cross-sectional design, and lack of evaluation for other inflammatory markers (like cytokines). These problems will be addressed in future studies.

Overall, levels of hs-CRP, IL-1β and IL-6 are associated with the development of PD. PD patients usually have higher levels of hs-CRP, IL-1β and IL-6 than the healthy subjects, which may be a cause for the neuroinflammation and neurodegenerative changes in PD. Early intervention can prevent the development and progression of peripheral nerve injuries.

Fund support

Fund name: Supported by the scientific research fund of Hebei Provincial Health Commission (Fund N.O: 20210310)

Hebei Provincial Department of Science and Technology Minsheng Science and Technology Special Project Supported by Hebei Provincial Key R&D Plan (Fund N.O: 20377721D).

References

1. Karpenko MN, Vasilishina AA, Gromova EA, Muruzheva ZM, Miliukhina IV, Bernadotte A. Interleukin-1β, interleukin-1 receptor antagonist, interleukin-6, interleukin-10, and tumor necrosis factor-α levels in CSF and serum in relation to the clinical diversity of Parkinson's disease. Cell Immunol 2018; 327: 77-82. https://doi.org/10.1016/j.cellimm.2018.02.011
2. Chen Z, Li G, Liu J. Autonomic dysfunction in Parkinson's disease: Implications for pathophysiology, diagnosis, and treatment. Neurobiol Dis 2020; 134: 104700. https://doi.org/10.1016/j.nbd.2019.104700
3. Li K, Reichmann H, Ziemssen T. Recognition and treatment of autonomic disturbances in Parkinson's disease. Expert Rev Neurother 2015; 15(10): 1189-203. https://doi.org/10.1586/14737175.2015.1095093
4. Bessler H, Djaldetti R, Salman H, Bergman M, Djaldetti M. IL-1 beta, IL-2, IL-6 and TNF-alpha production by peripheral blood mononuclear cells from patients with Parkinson's disease. Biomed Pharmacother 1999; 53(3): 141-5. https://doi.org/10.1016/S0753-3322(99)80079-1
5. Rees K, Stowe R, Patel S, Ives N, Breen K, Clarke CE, Ben-Shlomo Y. Non-steroidal anti-inflammatory drugs as disease-modifying agents for Parkinson's disease: evidence from observational studies. Cochrane Database Syst Rev 2011; (11): CD008454. https://doi.org/10.1002/14651858.CD008454.pub2
6. Liu P, Sun L, Zhao XL, Zhang P, Zhao XM, Zhang J. PAR2-mediated epigenetic upregulation of α-synuclein contributes to the pathogenesis of Parkinson's disease. Brain Res 2014; 1565: 82-9. https://doi.org/10.1016/j.brainres.2014.04.014
7. Ye L, Huang Y, Zhao L, Li Y, Sun L, Zhou Y, Qian G, Zheng JC. IL-1β and TNF-α induce neurotoxicity through glutamate production: a potential role for neuronal glutaminase. J Neurochem 2013; 125(6): 897-908. https://doi.org/10.1111/jnc.12263
8. Muñoz A, Garrido-Gil P, Dominguez-Meijide A, Labandeira-Garcia JL. Angiotensin type 1 receptor blockage reduces l-dopa-induced dyskinesia in the 6-OHDA model of Parkinson's disease. Involvement of vascular endothelial growth factor and interleukin-1β. Exp Neurol 2014; 261: 720-32. https://doi.org/10.1016/j.expneurol.2014.08.019
9. Menza M, Dobkin RD, Marin H, Mark MH, Gara M, Bienfait K, Dicke A, Kusnekov A. The role of inflammatory cytokines in cognition and other non-motor symptoms of Parkinson's disease. Psychosomatics 2010; 51(6): 474-9. https://doi.org/10.1176/appi.psy.51.6.474
10. Li D, Song X, Huang H, Huang H, Ye Z. Association of Parkinson's disease-related pain with plasma interleukin-1, interleukin-6, interleukin-10, and tumour necrosis factor-α. Neurosci Lett 2018; 683: 181-4. https://doi.org/10.1016/j.neulet.2018.07.027
11. Rothaug M, Becker-Pauly C, Rose-John S. The role of interleukin-6 signaling in nervous tissue. Biochim Biophys Acta 2016; 1863(6 Pt A): 1218-27. https://doi.org/10.1016/j.bbamcr.2016.03.018
12. Ting EY, Yang AC, Tsai SJ. Role of Interleukin-6 in Depressive Disorder. Int J Mol Sci 2020; 21(6): 2194. https://doi.org/10.3390/ijms21062194
13. Gasecka A, Siwik D, Gajewska M, Jaguszewski MJ, Mazurek T, Filipiak KJ, Postuła M, Eyileten C. Early Biomarkers of Neurodegenerative and Neurovascular Disorders in Diabetes. J Clin Med 2020; 9(9): 2807. https://doi.org/10.3390/jcm9092807
14. Nadrowski P, Chudek J, Skrzypek M, Puzianowska-Kuźnicka M, Mossakowska M, Więcek A, Zdrojewski T, Grodzicki T, Kozakiewicz K. Associations between cardiovascular disease risk factors and IL-6 and hsCRP levels in the elderly. Exp Gerontol 2016; 85: 112-7. https://doi.org/10.1016/j.exger.2016.10.001
15. Gorska-Ciebiada M, Ciebiada M. Association of hsCRP and vitamin D levels with mild cognitive impairment in elderly type 2 diabetic patients. Exp Gerontol 2020; 135: 110926. https://doi.org/10.1016/j.exger.2020.110926
16. Saba RA, Maia DP, Cardoso FEC, Borges V, F Andrade LA, Ferraz HB, Barbosa ER, Rieder CRM, da Silva DJ, Chien HF, Capato T, Rosso AL, Souza Lima CF, Bezerra JMF, Nicaretta D, Povoas Barsottini OG, Godeiro-Júnior C, Broseghini Barcelos L, Cury RG, Spitz M, Azevedo Silva SMC, Della Colletta MV. Guidelines for Parkinson's disease treatment: consensus from the Movement Disorders Scientific Department of the Brazilian Academy of Neurology - motor symptoms. Arq Neuropsiquiatr. 2022 Mar;80(3):316-329. doi: 10.1590/0004-282X-ANP-2021-0219. PMID: 35319667; PMCID: PMC9648930.

17. Koprich JB, Reske-Nielsen C, Mithal P, Isacson O. Neuroinflammation mediated by IL-1beta increases susceptibility of dopamine neurons to degeneration in an animal model of Parkinson's disease. J Neuroinflammation 2008; 5: 8. https://doi.org/10.1186/1742-2094-5-8
18. Mogi M, Harada M, Narabayashi H, Inagaki H, Minami M, Nagatsu T. Interleukin (IL)-1 beta, IL-2, IL-4, IL-6 and transforming growth factor-alpha levels are elevated in ventricular cerebrospinal fluid in juvenile parkinsonism and Parkinson's disease. Neurosci Lett 1996; 211(1): 13-6. https://doi.org/10.1016/0304-3940(96)12706-3
19. Mogi M, Harada M, Kondo T, Riederer P, Inagaki H, Minami M, Nagatsu T. Interleukin-1 beta, interleukin-6, epidermal growth factor and transforming growth factor-alpha are elevated in the brain from parkinsonian patients. Neurosci Lett 1994; 180(2): 147-50. https://doi.org/10.1016/0304-3940(94)90508-8
20. Hunot S, Dugas N, Faucheux B, Hartmann A, Tardieu M, Debré P, Agid Y, Dugas B, Hirsch EC. FcepsilonRII/CD23 is expressed in Parkinson's disease and induces, in vitro, production of nitric oxide and tumor necrosis factor-alpha in glial cells. J Neurosci 1999; 19(9): 3440-7. https://doi.org/10.1523/JNEUROSCI.19-09-03440.1999
21. Chang CP, Wu KC, Lin CY, Chern Y. Emerging roles of dysregulated adenosine homeostasis in brain disorders with a specific focus on neurodegenerative diseases. J Biomed Sci 2021; 28(1): 70. https://doi.org/10.1186/s12929-021-00766-y
22. Zhang J, Liu X, Wan C, Liu Y, Wang Y, Meng C, Zhang Y, Jiang C. NLRP3 inflammasome mediates M1 macrophage polarization and IL-1β production in inflammatory root resorption. J Clin Periodontol 2020; 47(4): 451-60. https://doi.org/10.1111/jcpe.13258
23. Stojakovic A, Paz-Filho G, Arcos-Burgos M, Licinio J, Wong ML, Mastronardi CA. Role of the IL-1 Pathway in Dopaminergic Neurodegeneration and Decreased Voluntary Movement. Mol Neurobiol 2017; 54(6): 4486-95. https://doi.org/10.1007/s12035-016-9988-x
24. Kuter K, Olech Ł, Głowacka U. Prolonged Dysfunction of Astrocytes and Activation of Microglia Accelerate Degeneration of Dopaminergic Neurons in the Rat Substantia Nigra and Block Compensation of Early Motor Dysfunction Induced by 6-OHDA. Mol Neurobiol 2018; 55(4): 3049-66. https://doi.org/10.1007/s12035-017-0529-z
25. Ferrari CC, Pott Godoy MC, Tarelli R, Chertoff M, Depino AM, Pitossi FJ. Progressive neurodegeneration and motor disabilities induced by chronic expression of IL-1beta in the substantia nigra. Neurobiol Dis 2006; 24(1): 183-93. https://doi.org/10.1016/j.nbd.2006.06.013
26. Jaafer, H., Kamac, M., Al-Gebori, A. Study of thyroid hormones effect on biochemical parameters of liver function in Iraqi patients. Cell Mol Biomed Rep 2023; 3(1): 29-34. doi: 10.55705/cmbr.2022.365507.1072
27. Taga T, Kishimoto T. Gp130 and the interleukin-6 family of cytokines. Annu Rev Immunol 1997; 15: 797-819. https://doi.org/10.1146/annurev.immunol.15.1.797
28. Almolda B, Villacampa N, Manders P, Hidalgo J, Campbell IL, González B, Castellano B. Effects of astrocyte-targeted production of interleukin-6 in the mouse on the host response to nerve injury. Glia 2014; 62(7): 1142-61. https://doi.org/10.1002/glia.22668
29. Monsour M, Croci DM, Grüter BE, Taussky P, Marbacher S, Agazzi S. Cerebral Aneurysm and Interleukin-6: a Key Player in Aneurysm Generation and Rupture or Just One of the Multiple Factors? Transl Stroke Res 2022. https://doi.org/10.1007/s12975-022-01079-4
30. Amanollahi M, Jameie M, Heidari A, Rezaei N. The Dialogue Between Neuroinflammation and Adult Neurogenesis: Mechanisms Involved and Alterations in Neurological Diseases. Mol Neurobiol 2023; 60(2): 923-59. https://doi.org/10.1007/s12035-022-03102-z
31. Singh S, Mishra A, Bharti S, Tiwari V, Singh J, Parul, Shukla S. Glycogen Synthase Kinase-3β Regulates Equilibrium Between Neurogenesis and Gliogenesis in Rat Model of Parkinson's Disease: A Crosstalk with Wnt and Notch Signaling. Mol Neurobiol 2018; 55(8): 6500-17. https://doi.org/10.1007/s12035-017-0860-4
32. Zhang Y, Cao H. Monomeric C-reactive protein affects cell injury and apoptosis through activation of p38 mitogen-activated protein kinase in human coronary artery endothelial cells. Bosn J Basic Med Sci 2020; 20(4): 487-94. https://doi.org/10.17305/bjbms.2020.4711
33. Nawaz MI, Mohammad G. Role of high-mobility group box-1 protein in disruption of vascular barriers and regulation of leukocyte-endothelial interactions. J Recept Signal Transduct Res 2015; 35(4): 340-5. https://doi.org/10.3109/10799893.2014.984309
34. Liu J, Yin W, Zhou C, Zhu Y, Gu M, Liu B, Ren H, Yang X. Association between levels of high-sensitivity C-reactive protein in plasma and freezing of gait in Parkinson's disease. Aging Clin Exp Res 2022; 34(8): 1865-72. https://doi.org/10.1007/s40520-022-02134-8
35. Ozdemir HS, Yunusoglu O, Sagmanligil V, Yasar S, Colcimen N, Goceroglu R, Catalkaya E. Investigation of the pharmacological, behavioral, and biochemical effects of boron in parkinson-indicated rats: Effects of Boron on Rotenone-Induced Parkinson's Disease. Cell Mol Biol (Noisy-le-grand). 2022 Aug. 3;68(8):13-21. doi: 10.14715/cmb/2022.68.8.3
36. Baran A, Bulut M, Kaya MC, Demirpençe Ö, Sevim B, Akıl E, Varol S. High-sensitivity C-reactive protein and high mobility group box-1 levels in Parkinson's disease. Neurol Sci 2019; 40(1): 167-73. https://doi.org/10.1007/s10072-018-3611-z