Neurological Sciences (2019) 40:167–173
https://doi.org/10.1007/s10072-018-3611-z

ORIGINAL ARTICLE

High-sensitivity C-reactive protein and high mobility group box-1 levels in Parkinson's disease

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Received: 11 May 2018 / Accepted: 17 October 2018 / Published online: 23 October 2018

Abstract

Various immunologic and inflammatory factors are contributed to pathogenesis of Parkinson's disease (PD). High mobility group box-1 (HMGB1) is a protein that plays certain roles in inflammation, DNA repair, transcription, somatic recombination, cell differentiation, cell migration, neuronal development, and neurodegeneration. The aim of the present study was to evaluate the serum levels of HMGB1 and high-sensitivity C-reactive protein (hs-CRP) among patients with Parkinson's disease and healthy controls. This study includes 30 patients with PD and 30 healthy controls, matched sex, age, body mass index, and smoking status. HMGB1 and hs-CRP serum levels were compared between the groups. The diagnostic performance of HMGB1 and hs-CRP was evaluated with receiver operating characteristic (ROC) curve analysis. HMGB1 levels were significantly higher in PD patients than in controls. Hs-CRP levels were significantly higher in PD patients than in controls There was a moderate correlation between hs-CRP and HMGB1 levels in the patient group. The cut-off value of HMGB1 level for the prediction of PD was determined as 32.8 ng/mL with 80% sensitivity and 60% specificity ($p = 0.006$). The cut-off value of hs-CRP level for the prediction of PD was determined as 0.63 mg/L with 66.7% sensitivity and 77.7% specificity ($p = 0.007$). This study demonstrates for the first time the association between HMGB1, hs-CRP, and PD. We found that HMGB1 and hs-CRP levels to be significantly higher in the PD patients than in the normal controls. As a result of the ROC curve analysis, HMGB1 and hs-CRP levels may be fair markers in the diagnosis of PD.

Keywords Parkinson's disease · High mobility group box-1 · High-sensitivity C-reactive protein · Inflammation

Introduction

Parkinson's disease is a chronic, progressive, neurodegenerative disease with a prevalence of approximately 0.3% in the population aged above 40 years [1]. Intranuclear Lewy bodies are observed in the brains of patients with Parkinson's disease. The neuronal loss in the substantia nigra pars compacta region of the midbrain and the decreased dopamine levels in the basal ganglia play significant roles in the pathophysiology of the disease [2]. Although the etiology of PD has not been entirely clarified, several environmental and genetic mechanisms are believed to be involved in progressive neurodegenerative process of PD [2, 3]. There are a growing number of the evidences which support the key role of neuroinflammation in PD pathogenesis [4].

Cytokines such as IL-1, IL-2, IL-4, IL-6, IL-10, IL-17, IL-18 TNF-α, IFN-γ, TGF-α, and MMP-3 play roles as immunologic and inflammatory factors, while immune cells, e.g., microglia, monocyte, NK cell, T cells, and B cells, also take part in disease pathophysiology [5].

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High mobility group box-1 (HMGB1) is a 30 KDa molecular-weight protein which predominantly exists in the cytoplasm of the liver and brain cells while presents both in cytoplasm and nucleus of the lymphoid cells [6–8]. HMGB1 plays specific roles in inflammation, DNA repair, transcription, somatic recombination and cell differentiation, and cell migration [7–9]. In addition, HMGB1, released from activated macrophages, can act as a cytokine and activate the other immune cells [10]. Furthermore, HMGB1 is believed to play a significant role in activation of pro-inflammatory mediators, such as TNF-α, IL-1β, and IL-8 [11, 12].

HMGB1 also plays an important role in neuronal development and neurodegeneration. HMGB1 induces neuroinflammation after spine and brain injuries in adults [13]. The levels of endogenous HMGB1 were found to be elevated in the presence of neurodegenerative disorders. In other neurodegenerative diseases, such as Alzheimer's disease and multiple sclerosis, HMGB1 is defined as a risk factor for progression of memory disorders, chronic neurodegeneration, and neuroinflammation [14, 15].

C-reactive protein (CRP), composed of five 23 kDa subunits, is a hepatically derived pentraxin that has a crucial role in the human immune system [16]. CRP level is a useful non-specific biochemical marker of inflammation and makes important contributions during the screening of organ diseases and the monitoring of responses to treatment in the cases of inflammation and infection. C-reactive protein levels measured using highly sensitive techniques (hs-CRP) are convenient and sensitive markers of inflammatory activity in clinical practice. Hs-CRP and fibrinogen have been most frequently studied as potential biomarkers of systemic inflammation [17]. Recent reports have shown that elevated hs-CRP levels independently predict the risk of future cardiovascular disease and ischemic cerebrovascular disease in the elderly [18]. Many previous studies have suggested that high concentrations of hs-CRP are associated with increased risk of cerebrovascular and neurodegenerative diseases because hs-CRP increases the paracellular permeability of the blood-brain barrier (BBB) when its concentration exceeds the threshold required to impair BBB function. CRP, a marker of chronic inflammation, has been detected in the senile plaques and neurofibrillary tangles of patients with Alzheimer's disease [15, 19]. Previous studies reported elevated hs-CRP levels in PD patients compared to healthy controls [17, 20]. However, a limited number of studies investigated HMGB1 levels in PD patients [21]. To contribute to the literature, in the present study, we aimed to describe the roles of hs-CRP and HMGB1 in PD pathophysiology by comparing their levels in patients diagnosed with PD and healthy controls.

Material and methods

Subjects

Patient and control groups

The study population consisted of patients with a diagnosis of Parkinson's disease, who were referred to the Dicle University Neurology Outpatient Clinics between March and December 2013, and healthy controls. All participants were evaluated by a neurologist.

A total number of 39 patients were referred to neurology outpatient clinics and were diagnosed with idiopathic Parkinson's disease based on UK Parkinson's disease Brain Bank [19] criteria. Thirty patients who met the eligibility criteria were included in this study. Hoehn and Yahr [22] staging scale (H & Y stage) was used for clinical staging of the disease. Control group consisted of 30 healthy subjects who were selected among the individuals referring to the hospital's blood bank for blood donation, who had no neurological or infectious disease, and who met study eligibility criteria. Control group was matched with the patient group regarding sociodemographic characteristics and smoking status. Several toxins present in cigarette smoke have immunomodulatory effects [23]. Therefore, the potential confounding effects of factors, such as age, gender, smoking, and BMI on HMGB1, and hs-CRP levels, were eliminated.

Patients who had a comorbid neurological disorder, an inflammatory or autoimmune disorder, or an active infection, who are pregnant, patients with a severe systemic disease, diabetes mellitus, chronic heart disease, liver or kidney failure, alcohol or substance abuse, a history of severe head trauma, patients who had a surgical operation or myocardial infarction within the last 6 months, patients with mental retardation, patients using vitamin or fish oil, and patients using medications that affect the immune system, such as steroids, were excluded from this study.

After all participants signed the informed consent form, data were collected using a sociodemographic data collection form. Blood samples were obtained for biochemical analyses.

Blood sampling and measurement of serum HMGB1 levels

Venous blood samples were obtained from all participants at 8.00 a.m. after 12 h of fasting. Blood samples were centrifuged at 3000 rpm for 10 min to separate the plasma. Collected plasma samples were stored at − 80 °C until the time of analyses. HMGB1 levels were measured in the laboratories of the Dicle University Medical Faculty Department of Biochemistry. Serum

samples were thawed on the day of the experiment. Afterwards, samples were mixed by using vortex. Then, HMGB1 levels were assessed in a manually performed quantitative sandwich enzyme-linked immunosorbent assay (ELISA) assay kit, according to the manufacturer's instruction (Sunred Biological Technology Co., Ltd., Shanghai). HMGB1 levels were measured in ng/mL unit. High-sensitive C-reactive protein (hs-CRP) levels were measured in mg/L unit using nephelometric assay (Beckman Immage 800) method.

Statistical analyses

Data were analyzed by SPSS 15.0 statistical package software. The chi-square test was used to compare the frequencies and ratios of categorical variables. Continuous variables were presented as the mean ± standard deviation. Variables were checked to confirm if they were normally distributed. The *t* test was used to compare the mean values of normally distributed variables between two groups, while the mean values of non-normally distributed variables were compared by Mann-Whitney *U* test. Pearson correlation analysis was performed to evaluate potential correlations between different variables. Receiver operating characteristic (ROC) curve were constructed, area under the ROC curve (AUC) was calculated, and threshold values were estimated to detect sensitivity and specificity of Hs-CRP and HMGB1 levels for the diagnosis of Parkinson's disease. p values of < 0.05 were considered statistically significant.

Results

A total number of 30 patients diagnosed with Parkinson's disease and 30 healthy controls were included in this study. HMGB1 and hs-CRP levels, age, gender, BMI, and smoking status were compared between the patient and control groups. While HMGB1 and hs-CRP levels were significantly different between the patient and control groups, there was no significant difference regarding the other variables (Fig. 1).

Table 1 shows the results for HMGB1 and hs-CRP levels, age, gender, BMI, and smoking status in the patient and control groups.

In total, 6.7% ($n = 2$) of the patients had a family history of Parkinson's disease. None of the subjects in control group had a family history of Parkinson's disease. The mean of the Hoehn and Yahr scale scores of the patients was 3.3 ± 1.3. Mean disease duration was 5.9 ± 4.7 years (Table 1). The mean dose of levodopa was 470 ± 274 mg/day. MAO inhibitors were used by 43.3% ($n = 13$) of the patients. Levodopa + benserazide HCl were used by 90% ($n = 27$), and other dopamine agonists were used by 73.3% ($n = 22$) of the patients.

Correlation analyses of HMGB1, hs-CRP levels, age, and BMI in the patient group indicated that there was a correlation between hs-CRP and HMGB1 levels ($r = 0.528$, $p = 0.003$). A moderate correlation was also found between mean Hoehn and Yahr scale scores and levodopa dosage ($r = 0.578$, $p = 0.01$). There was no significant correlation between HMGB1, hs-CRP levels, age, BMI, disease severity, and duration of disease.

A cut-off HMGB1 value of 32.8 ng/mL was determined to predict PD with 80% sensitivity and 60% specificity (ROC AUC 0.707; 95% CI 0.571–0.844; $p = 0.006$) (Fig. 2.). A cut-off hs-CRP of 0.63 mg/L was found to predict PD with 66.7% sensitivity and 77.7% specificity (ROC AUC 0.701; 95% CI 0.555–0.847; $p = 0.007$ (Fig. 2).

Discussion

A limited number of studies investigated HMGB1 levels in humans with Parkinson's disease, and the present study

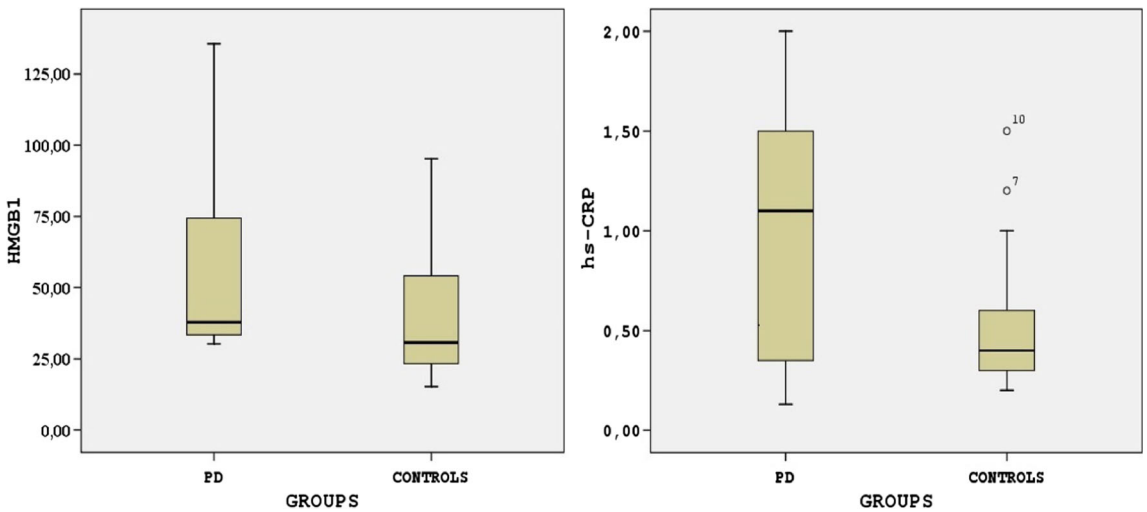

Fig. 1 Box-plot presentation of high mobility group box-1 (HMGB1) and high-sensitivity C-reactive protein (hs-CRP) in Parkinson's disease (PD) and healthy controls

Table 1 HMGB1 and hs-CRP levels, age, gender, BMI, and smoking status in the patient and control groups

	Patients ($n = 30$) mean ± SD	Controls ($n = 30$) mean ± SD	t	p
HMGB1 (ng/mL)	54.6 ± 32.1	39.2 ± 23.2	2.196	0.032
Hs-CRP (mg/L)	0.999 ± 604	0.515 ± 0.300	3.935	< 0.01
Age (year)	70.7 ± 9.6	66.8 ± 9.0	1.607	0.113
BMI	26.04 ± 5.03	25.12 ± 1.33	0.975	0.334
Hoen year score	3.3 ± 1.3	–	–	–
Disease duration (year)	5.9 ± 4.7	–	–	–
	Patients ($n = 30$) N (%)	Controls ($n = 30$) N (%)	X^2	p
Smoking status			0.111	0.739
Non-smoker	83.3 (25)	80 (24)		
Smoker	16.7 (5)	20 (6)		
Gender			0.267	0.606
Female	46.7 (14)	53.3 (16)		
Male	53.3 (16)	46.7 (14)		

$p < 0.05$, statistically significant

demonstrated that hs-CRP and HMGB1 levels were significantly higher in PD patients compared to healthy controls. This finding is consistent with the results of previous studies showing the contribution of HMGB1 to neurodegeneration [21, 24]. To our knowledge, no previous study investigated the relationship between hs-CRP and HMGB1 in the PD patients. A previous study, evaluated the relation between hs-CRP and HMGB1 in atherosclerosis, demonstrated that CRP activates macrophage (RAW264.7) cells through Fcγ receptor and p38MAPK [25]. In that study, CRP-mediated HMGB1 release was also found to be time and dose dependent. Besides, hs-CRP stimulation resulted in translocation of nuclear HMGB1 to the cytoplasm. Again, the same study showed that HMGB1 induced by hs-CRP was released from active macrophages but not from dead cells. Moreover, CRP

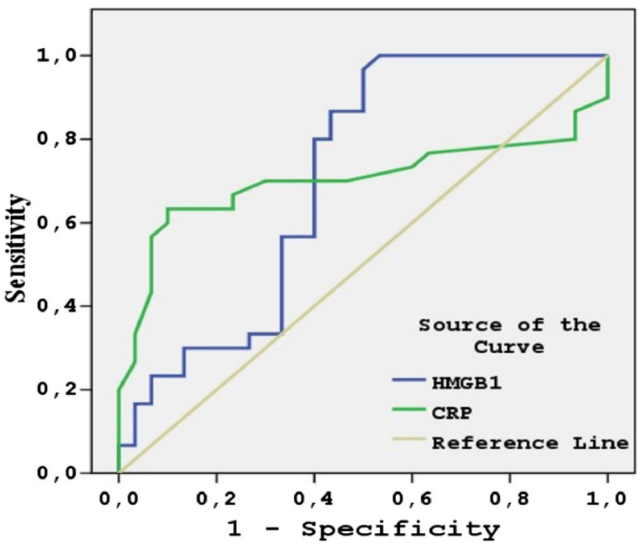

Fig. 2 The ROC curve analysis of hs-CRP and HMGB1 for prediction

levels measured in the presence of obesity and cardiovascular diseases were shown to cause significant HMGB1 release from the macrophages, which suggests that CRP may play a crucial role in several inflammatory systems [25]. In the present study, a moderate correlation was found out between hs-CRP and HMGB1 levels, which suggests that the increase in HMGB1 levels in PD is caused by some other mechanisms and not only by hs-CRP.

Only one previous study in the literature reported HMGB1 levels in animal model of PD [21]. Previous studies indicated that HMGB1 is a proinflammatory nuclear protein and passively released from necrotic cells and induces inflammation. Actively, it is released from the macrophages and monocytes through acetylation. When acetylation occurs, HMGB1 is translocated from the nucleus to the lysosomes. Extracellular HMGB1 shows cytokine-like effects on the RAGE receptors and Toll-like family of receptors. This, in turn, results in the release of several cytokines and chemo-attractants. Administration of HMGB1 antagonists to rats during lethal sepsis causes more extensive effects compared to the other cytokines [12, 24].

HMGB1 mediates vascular barrier dysfunctions by modulating expression of adhesion molecules on the endothelial cells, such as intercellular adhesion molecule-1, vascular cell adhesion protein-1, and E-selectin. This process results in leukocyte adhesion and migration from the endothelium, leading to disruption of vascular barrier (blood-brain barrier and blood-retina barrier) [26]. This finding suggests that similar to the effects of CRP, peripheral HMGB1 may elevate the HMGB1 levels in the brain by causing BBB dysfunction, and/or elevated HMGB1 levels in the brain may also affect peripheral HMGB1 levels by inducing BBB dysfunction (Fig. 3).

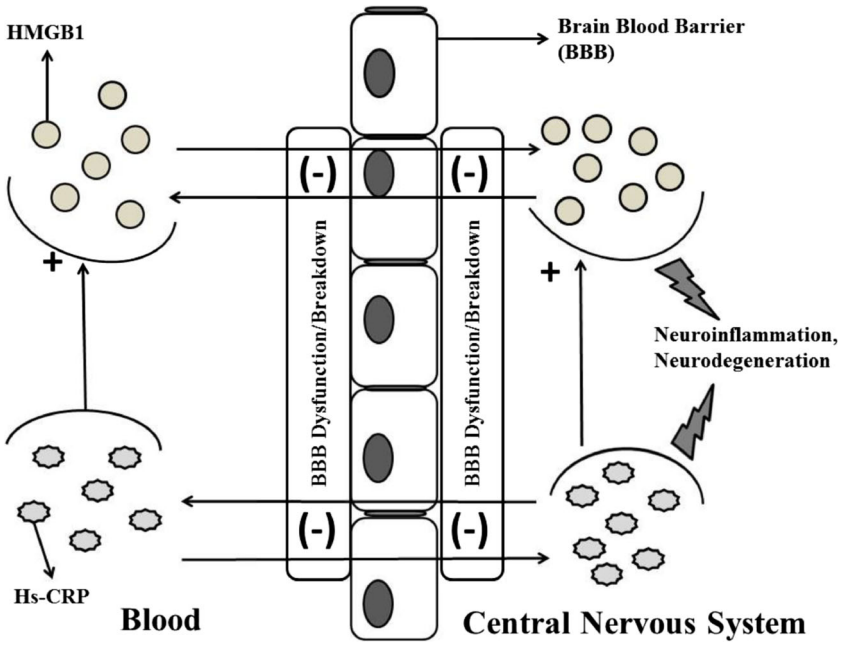

Fig. 3 The effects of HMGB1 and hs-CRP on the blood-brain barrier in Parkinson's disease

HMGB1, released from activated microglia and/or degenerated neurons, binds to microglial Mac1 (macrophage antigen complex-1) and inhibits NF-κB and NADPH oxidase pathway [15]. This results in chronic neuroinflammation and progressive dopaminergic neurodegeneration by stimulating the production of multiple inflammatory and neurotoxic factors. In a Parkinson's model stimulated in rats by 6-OHD, HMGB1 levels were found to be elevated in striatum and plasma in brain tissues. AntiHMGB1 monoclonal antibodies protected from inflammation cascade and showed therapeutic efficacy by neutralizing the released HMGB1. AntiHMGB1 antibodies decreased the increase in vascular permeability in BBB, which was induced by 6-OHD neurotoxicity. Following 6-OHDG injection, IL1B and IL-6 mRNA levels were found to be elevated in the striatum and SNc. These increases were also suppressed by AntiHMGB1 antibodies. AntiHMGB1 monoclonal antibodies provided neuroprotective effects. This study demonstrated that HMGB1 plays roles in both acute and chronic neurodegeneration [24]. In another study performed in a rat model with Parkinson's induced by MPTP, HMGB1 levels were found to be elevated, and antiHMGB1 antibody therapy reduced the neurotoxicity induced by MPTP [21].

Hs-CRP is a non-specific marker of low-grade systemic inflammation (21–5). Although hs-CRP plays a role in acute phase responses given to infections or organ injury, circulating hs-CRP levels indicates ongoing low-grade inflammation similar to that seen in the presence of atherosclerosis [25]. CRP passes the blood-brain barrier in trace amounts. However, concentrations above a certain threshold impair BBB functions by increasing paracellular permeability. This threshold is easily exceeded in conditions, such as obesity and systemic inflammation. Increased paracellular permeability results in the entrance of CRP into CNS, leading to reactive gliosis and CNS dysfunction. However, increased inflammatory proteins in the CNS results in an increase in the levels of peripheral inflammatory proteins by passing through the BBB, owing to increased permeability caused by neuroinflammation or stimulation of the production of peripheral inflammatory proteins [26]. In this case, the peripheral concentration of inflammatory proteins may reflect the neuroinflammatory changes in the CNS. Supporting the hypothesis that neuroinflammation plays a role in the pathophysiology of PD, there are previous studies in the literature that showed elevated hs-CRP levels in PD patients. In line with those studies, the present study showed that hs-CRP levels were significantly elevated in PD patients compared to healthy controls [17, 20, 27].

In the present study, we demonstrated the diagnostic performance of HMGB1 and hs-CRP as markers of neuroinflammation in PD. A cut-off HMGB1 value of 32.8 ng/mL was determined to predict PD with 80% sensitivity and 60% specificity (ROC AUC 0.707; 95% CI 0.571–0.844; $p = 0.006$) (Fig. 2). A cut-off hs-CRP of 0.63 mg/L was found to predict PD with 66.7% sensitivity and 77.7% specificity (ROC AUC 0.701; 95% CI 0.555–0.847; $p = 0.007$ (Fig. 2). At a result of ROC curve analysis, HMGB1 and hs-CRP levels considered to be "fair" at separating PD patients from healthy controls. PD is currently diagnosed based on physical examination findings. Biochemical markers are readily available for measurements and can provide non-invasive and objective tools aiding in prediction of disease progression and understanding of the mechanisms underlying Parkinson's disease. To our knowledge, there is still no specific biochemical marker for

the diagnosis of PD. New diagnostic performance tests are required for excluding other diseases. Our test is not specific for PD, and this is an important limitation of our study. Therefore, further studies are needed in this respect.

There are several limitations of our study such as small sample size, cross-sectional design, absence of analysis for sub groups of PD like early onset PD, and absence of the assessment of other inflammatory markers like cytokines. One another limitation of our study is that the inflammatory parameters measured in the circulation do not necessarily reflect local inflammation in the brain.

In conclusion, there is an association between HMGB1, hs-CRP, and PD. HMGB1 and hs-CRP levels were significantly higher in the PD patients than in the normal controls. A moderate correlation was found out between hs-CRP and HMGB1 levels, which suggests that the increase in HMGB1 levels in PD is caused by some other mechanisms and not only by hs-CRP. In final, increased hs-CRP and HMGB1 may disrupt BBB and lead to neuroinflammation and neurodegeneration in PD. At a result of ROC curve analysis, HMGB1 and hs-CRP levels may be useful markers for diagnosing PD.

Compliance with ethical standards

All investigators who took part in this study signed the Declaration of Helsinki, and this study was conducted after the necessary administrative permits and approval of local ethics committee was in place (Ethics committe approval number:720/20).

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Pringsheim T, Jette N, Frolkis A, Steeves TD (2014) The prevalence of Parkinson's disease: a systematic review and meta-analysis. Mov Disord 29(13):1583–1590. https://doi.org/10.1002/mds.25945
2. Hornykiewicz O (2006) The discovery of dopamine deficiency in the parkinsonian brain. J Neural Transm Suppl 70:9–15
3. Yang Y, Han CY, Guo L, Guan QB (2018) High expression of the HMGB1-TLR4 axis and its downstream signaling factors in patients with Parkinson's disease and the relationship of pathological staging. Brain Behav 8(4):e00948. https://doi.org/10.1002/brb3.948
4. Vivekanantham S, Shah S, Dewji R, Dewji A, Khatri C, Ologunde R (2015) Neuroinflammation in Parkinson's disease: role in neurodegeneration and tissue repair. Int J Neurosci 125(10):717–725. https://doi.org/10.3109/00207454.2014.982795
5. Chao Y, Wong SC, Tan EK (2014) Evidence of inflammatory system involvement in Parkinson's disease. Biomed Res Int 2014: 308654. https://doi.org/10.1155/2014/308654
6. Zhang J, McCauley MJ, Maher LJ 3rd, Williams MC, Israeloff NE (2009) Mechanism of DNA flexibility enhancement by HMGB proteins. Nucleic Acids Res 37(4):1107–1114. https://doi.org/10.1093/nar/gkn1011
7. Kang HJ, Lee H, Choi HJ, Youn JH, Shin JS, Ahn YH, Yoo JS, Paik YK, Kim H (2009) Non-histone nuclear factor HMGB1 is phosphorylated and secreted in colon cancers. Lab Investig 89(8): 948–959. https://doi.org/10.1038/labinvest.2009.47
8. Thomas JO, Travers AA (2001) HMG1 and 2, and related 'architectural' DNA-binding proteins. Trends Biochem Sci 26(3):167–174
9. Muller S, Scaffidi P, Degryse B, Bonaldi T, Ronfani L, Agresti A, Beltrame M, Bianchi ME (2001) New EMBO members' review: the double life of HMGB1 chromatin protein: architectural factor and extracellular signal. EMBO J 20(16):4337–4340. https://doi.org/10.1093/emboj/20.16.4337
10. Todorova J, Pasheva E (2012) High mobility group B1 protein interacts with its receptor RAGE in tumor cells but not in normal tissues. Oncol Lett 3(1):214–218. https://doi.org/10.3892/ol.2011.459
11. Park JS, Arcaroli J, Yum HK, Yang H, Wang H, Yang KY, Choe KH, Strassheim D, Pitts TM, Tracey KJ, Abraham E (2003) Activation of gene expression in human neutrophils by high mobility group box 1 protein. Am J Phys Cell Physiol 284(4):C870–C879. https://doi.org/10.1152/ajpcell.00322.2002
12. Tian J, Avalos AM, Mao SY, Chen B, Senthil K, Wu H, Parroche P, Drabic S, Golenbock D, Sirois C, Hua J, An LL, Audoly L, La Rosa G, Bierhaus A, Naworth P, Marshak-Rothstein A, Crow MK, Fitzgerald KA, Latz E, Kiener PA, Coyle AJ (2007) Toll-like receptor 9-dependent activation by DNA-containing immune complexes is mediated by HMGB1 and RAGE. Nat Immunol 8(5): 487–496. https://doi.org/10.1038/ni1457
13. Fang P, Schachner M, Shen YQ (2012) HMGB1 in development and diseases of the central nervous system. Mol Neurobiol 45(3): 499–506. https://doi.org/10.1007/s12035-012-8264-y
14. Lindersson EK, Hojrup P, Gai WP, Locker D, Martin D, Jensen PH (2004) alpha-Synuclein filaments bind the transcriptional regulator HMGB-1. Neuroreport 15(18):2735–2739
15. Gao HM, Zhou H, Zhang F, Wilson BC, Kam W, Hong JS (2011) HMGB1 acts on microglia Mac1 to mediate chronic neuroinflammation that drives progressive neurodegeneration. J Neurosci 31(3): 1081–1092. https://doi.org/10.1523/JNEUROSCI.3732-10.2011
16. Rizzi L, Marques FC, Rosset I, Moriguchi EH, Picon PD, Chaves ML, Roriz-Cruz M (2014) C-reactive protein and cognition are unrelated to leukoaraiosis. ScientificWorldJournal 2014:121679–121678. https://doi.org/10.1155/2014/121679
17. Song IU, Kim YD, Cho HJ, Chung SW (2013) Is neuroinflammation involved in the development of dementia in patients with Parkinson's disease? Intern Med 52(16):1787–1792
18. Kuo HK, Yen CJ, Chang CH, Kuo CK, Chen JH, Sorond F (2005) Relation of C-reactive protein to stroke, cognitive disorders, and depression in the general population: systematic review and meta-analysis. Lancet Neurol 4(6):371–380. https://doi.org/10.1016/S1474-4422(05)70099-5
19. Hughes AJ, Daniel SE, Kilford L, Lees AJ (1992) Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 55(3):181–184
20. Song IU, Chung SW, Kim JS, Lee KS (2011) Association between high-sensitivity C-reactive protein and risk of early idiopathic Parkinson's disease. Neurol Sci 32(1):31–34. https://doi.org/10.1007/s10072-010-0335-0
21. Santoro M, Maetzler W, Stathakos P, Martin HL, Hobert MA, Rattay TW, Gasser T, Forrester JV, Berg D, Tracey KJ, Riedel G, Teismann P (2016) In-vivo evidence that high mobility group box 1 exerts deleterious effects in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine model and Parkinson's disease which can be attenuated by glycyrrhizin. Neurobiol Dis 91:59–68. https://doi.org/10.1016/j.nbd.2016.02.018
22. Hoehn MM, Yahr MD (1967) Parkinsonism: onset, progression and mortality. Neurology 17(5):427–442
23. Lee J, Taneja V, Vassallo R (2012) Cigarette smoking and inflammation: cellular and molecular mechanisms. J Dent Res 91(2):142–149. https://doi.org/10.1177/0022034511421200
24. Sasaki T, Liu K, Agari T, Yasuhara T, Morimoto J, Okazaki M, Takeuchi H, Toyoshima A, Sasada S, Shinko A, Kondo A,

Kameda M, Miyazaki I, Asanuma M, Borlongan CV, Nishibori M, Date I (2016) Anti-high mobility group box 1 antibody exerts neuroprotection in a rat model of Parkinson's disease. Exp Neurol 275(Pt 1):220–231. https://doi.org/10.1016/j.expneurol.2015.11.003

25. Kawahara K, Biswas KK, Unoshima M, Ito T, Kikuchi K, Morimoto Y, Iwata M, Tancharoen S, Oyama Y, Takenouchi K, Nawa Y, Arimura N, Jie MX, Shrestha B, Miura N, Shimizu T, Mera K, Arimura S, Taniguchi N, Iwasaka H, Takao S, Hashiguchi T, Maruyama I (2008) C-reactive protein induces high-mobility group box-1 protein release through activation of p38MAPK in macrophage RAW264.7 cells. Cardiovasc Pathol 17(3):129–138. https://doi.org/10.1016/j.carpath.2007.08.006
26. Nawaz MI, Mohammad G (2015) Role of high-mobility group box-1 protein in disruption of vascular barriers and regulation of leukocyte-endothelial interactions. J Recept Signal Transduct Res 35(4):340–345. https://doi.org/10.3109/10799893.2014.984309
27. Akil E, Bulut A, Kaplan I, Ozdemir HH, Arslan D, Aluclu MU (2015) The increase of carcinoembryonic antigen (CEA), high-sensitivity C-reactive protein, and neutrophil/lymphocyte ratio in Parkinson's disease. Neurol Sci 36(3):423–428. https://doi.org/10.1007/s10072-014-1976-1