ISSN: 2688-8653

Research Progress on the Correlation Between Depression and Cognitive Impairment in Parkinson's Disease

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Abstract

Depression and cognitive impairment, as common non-motor symptoms of Parkinson's disease, are often accompanied clinically. In many fields of cognition, depression most affects executive function in cognitive function, which also shows that there is a certain connection between depression and cognitive function, and a large number of research data also support this view. However, the pathways and mechanisms of the interaction between depression and cognitive impairment have not yet been clinically clarified.This article summarizes the related mechanisms, potential biomarkers and treatments of depression and cognitive impairment in Parkinson's disease to gain a deeper understanding of the relationship between the two.

Keywords

Parkinson's disease; Depression; Cognitive impairment.

1. Introduction

Parkinson's disease, a progressive neurodegenerative disease characterized by tremor and bradykinesia, is a common neurological disorder [1]. The global prevalence of PD is estimated to be approximately 6.1 million people, and with increased life expectancy, the prevalence is increasing further worldwide [2]. PD is mainly defined and diagnosed by its motor symptoms, including tremor, bradykinesia, and muscle rigidity, and clinical attention is not only motor dysfunction, but also the diagnosis and treatment of non-motor symptoms [3]. Patients with PD develop neuropsychiatric disorders, including depression, anxiety, sleep disturbances, and cognitive impairment, during or even before the disease progresses [4]. Among them, depression and cognitive impairment are common and attention-worthy non-motor symptoms in patients with PD, on the one hand, depression often precedes motor symptoms and is difficult to diagnose clinically, and on the other hand, they are associated with high morbidity, disability, and mortality as the disease progresses [5,6]. In addition, depression and cognitive impairment place a greater burden on patients and caregivers than motor symptoms. Clinical studies have found [7] that depression and cognitive impairment are related to each other and affect each other, but the potential mechanism of the two associations needs to be further studied.

2. Depression in PD

Patients with DPD are clinically manifested as lack of interest in things, loss of sources of pleasure, slowing of psychomotor, etc., similar to typical depression. However, because they do not feel defeated, the risk of suicide is lower than in people with simple depression [8,9]. Prevalence fluctuates widely depending on how studies assess it, and the prevalence of clinically significant depressive symptoms is approximately 35 percent [10]. In addition, the effects of dopaminergic medications in PD patients and the overlap of depressive symptoms with some PD symptoms (eg, decreased facial expressions) make the diagnosis of DPD and the classification of depression more difficult [11]. There are currently nine scales used in clinical

ISSN: 2688-8653

clinical evaluation of DPD, of which the geriatric depression scale (GDS-30) is considered to be the most effective screening tool for DPD, and the most commonly used is the hamilton depression scale (HAMD) [12,13]. Factors influencing DPD include motor complications, disease stage and duration, sleep disturbance, anxiety, and cognitive impairment [14]. The currently accepted model of DPD development is that the degeneration of dopaminergic neurons in the mesocortex and midbrain margin leads to orbitofrontal dysfunction, which destroys serotonergic neurons in the dorsal midsuture and leads to dysfunction of the orbitofrontal-basal ganglia-thalamic circuit associated with depression [5,15].

3. PD with cognitive impairment

The incidence and severity of cognitive impairment, one of the common non-motor symptoms in PD, increase with the progression of PD [16]. It has been reported [17] that approximately 20–33% of patients already have mild cognitive impairment (MCI) at the time of diagnosis of PD, and 60%–80% can progress to Parkinson's disease dementia (PDD) within 12 years. The cognitive domain is divided into six main components (overall cognition, memory, executive function, attention and working memory, visuospatial function, and language), of which memory and executive deficits are the most common and core impairment features of PDCI, while impaired attention is the strongest evidence to distinguish PDD from Alzheimer's disease (AD) [18]. As a node in the cognitive impairment process, PD-MCI partially deteriorates into PDD and partially reverses to normal cognition [19,20], so early intervention is necessary. Risk factors for cognitive impairment include advanced age, low level of education, movement disorders, depression, and apathy, among which DPD patients with low education are more likely to negatively affect cognition [21,22]. The pathological mechanism of PDCI is complex and unclear, including the reduction of the level of various neurotransmitters, the disruption of the amygdala-hippocampal pathway, and the frontal cortex-basal ganglia-thalamic ring [23].

4. Clinical evidence associated with DPD and PDCI

In a case-control study of 100 PD patients, Sinaeefar et al. [24] showed that there was a significant relationship between depressive symptoms in PD patients and the degree of cognitive impairment. Park Zhihao et al. [25] followed PD patients for up to 4 years, and through multivariate COX regression analysis, it was shown that depression is an independent risk factor for PD patients with normal cognitive function to switch to PD-MCI, and depression in the early stage of PD may be related to cortical atrophy of PD-MCI. Forbes et al. [26] found that patients with PD with depressive symptoms had lower scores on the Montreal Cognitive Assessment (MoCA). Jones et al. [27] also found that depression can aggravate the impairment of working memory, learning, and delayed recall in PD patients. Wu Aiqin et al. [28] through the clock drawing test (CDT), the trail making test (TMT) and other examinations, showed that depression can damage PD patients' sustained attention, verbal working memory, etc., which are related to executive function (EF) in cognitive function. Chen Jing et al. [29] conducted multiple linear regression analysis, and the results showed that depression had a positive predictive effect on cognitive impairment, especially EF damage.

5. Relevance of pathogenesis

5.1. Damage to neurotransmitters

Modern research believes [30], DPD and PDCI have a common pathological mechanism, depression aggravates neurodegeneration, destroys conduction pathways (such as frontal-striatum circuit, amygdala-hippocampal circuit, etc.), thereby inducing PDCI and even leading to more serious cognitive impairment. The role of neurotransmitters such as dopamine (DA),

ISSN: 2688-8653

norepinephrine (NE), serotonin (5-hydroxytryptamine, 5-HT), and adenosine is more prominent.

5.1.1. DA

Studies [31,32] have clearly shown that the lack of DA in the striatum in PD patients is associated with EF in the cognitive domain and poor language and visual ability; Depression in PD patients is negatively correlated with dopamine transporter (DAT) binding, and lower DAT binding is thought to reflect severe degeneration of striatal dopaminergic neurons, resulting in decreased DA levels in the striatum. The destruction of DA neurons in the substantia nigra (SN) can also lead to damage to the frontal-striatum circuit, which plays an important role in regulating various functions such as mood and cognitive function. At the same time, the midbrain limbic and midbrain cortical dopaminergic pathways mediate affective, behavioral, and cognitive, and damage to this pathway can exacerbate depression and cognitive impairment. Wei Ke et al. [33] analyzed the serum DA levels of each group and scored them on the HAMAD scale, and finally concluded that the serum DA levels of patients in the DPD group were significantly lower than those in the NPD (nondepression in PD) group and the healthy group, and the total HAMAD score and DA level of the patients were negatively correlated with the degree of depression.

5.1.2. NE

Neuropathology and neuroimaging studies have shown [34] that NE neurons in locus coeruleus (LC) degenerate earlier than DA damage in midbrain SN, which is likely to be related to the earlier onset of non-motor symptoms such as olfactory loss and depression in PD patients. The degeneration of neurons will damage the noradrenergic pathway, so that the NE in the prefrontal cortex (PFC) is at a low level, reducing the response to sensory conduction, impairing cognitive flexibility and aggravating attention deficits; Interrupting NE projections originating in the forebrain α, β adrenergic receptors fail to activate, eventually leading to cognitive and behavioral deficits. Decreased transmission function of norepinephrine nerves is also one of the pathological phenomena that lead to depression and poor EF in PD patients. In addition, NE enhances memory accuracy and pleasure by enhancing the connectivity of the basolateral amygdala to the hippocampus, resulting in long-lasting hippocampus-dependent episodic-like memories and positive emotions. Teredici et al. [35] believe that intervention treatment for NE can not only alleviate the state of depression and anxiety in PD patients, but also delay cognitive decline.

5.1.3. 5-HT

The 5-HT system is both a regulator of γ-aminobutyric acid and glutamatergic activity, and one of the essential neurotransmitters in the relay station of direct and indirect activation of the striatum-thalamic cortical pathway, playing an important role in involving cognition and emotions. Especially when PFC receives 5-HT from the dorsal and median lobes is reduced, making PFC immune to cognitive (especially executive function) and emotion regulation disorders. Zhu Wenming et al. [36] found that before treatment, the serum 5-HT level of patients in the DPD group decreased compared with the nPD group, and the proportion of MoCA total score and ≥ 26 points also decreased compared with the nPD group, and after 3 months of treatment, the serum 5-HT level of patients with a total MoCA score of ≥ 26 points was significantly higher than that of patients with a total score of less than 26 points of MoCA. Shao Ziqiang et al. [37] measured the platelet 5-HT levels of PD patients and healthy people, and found that the platelet 5-HT levels of PD patients were significantly lower than those in healthy people, the HAMAD scale score was higher, and the mini mental status examination (MMSE) was lower, indicating that the platelet 5-HT levels of DPD and PDCI patients were lower.

ISSN: 2688-8653

5.1.4. Adenosine

Jakova et al. [38] clearly show that adenosine can directly interact with α-synuclein to regulate α-synuclein aggregation and neurodegeneration of DA neurons in SN. Among them, adenosine A2 amperoreceptors can address some neuropsychiatric components of non-motor symptoms - specifically cognitive impairment, depression, and excessive daytime sleepiness. Adenosine A2 receptors are located primarily on the indirect γ-GABA-ergostriatum output pathway, but are also present to some extent in marginal areas of the brain, particularly the nucleus accumbens, but also in the thalamus and neocortex, and there is some evidence that increased activity of these receptors is associated with cognitive deterioration. Extensive studies have shown [39] that adenosine A2A antagonists may be effective in improving cognition in PD or even reversing cognitive deficits by increasing the DA activity of PFCs in a series of experimental models associated with early execution and visuospatial deficits in PD. Similarly, A2 amperometric receptor antagonists can reverse depressive symptoms in experimental models of PD, including models with high predictive value in humans, and to the same extent as classical antidepressants.

5.2. Neuroinflammation and immune response

There is growing evidence [40,41] of a link between inflammatory responses mediated by pro-inflammatory cytokines and autoimmunity and altered cognition and mood. Autopsy studies have shown an increase in pro-inflammatory cytokines such as interferon (IFN)-γ, tumor necrosis factor (TNF)-α, interleukin IL-1β, and IL-6 in the PD brain. The presence of pro-inflammatory cytokines and α-synuclein aggregates can trigger microglia activation, and activated microglia can further release a variety of neuroinflammatory mediators, trigger stronger inflammatory responses and exacerbate the neurodegeneration of PD, among which DA in SN dense is particularly susceptible to microglia-mediated neurotoxicity. In addition to brain tissue, elevated levels of TNF-α, IL-6, and IL-1β were found in the cerebrospinal fluid of patients with PD. Plasma TNF-α levels are inversely associated with depressive symptoms and cognitive performance, and higher IL-6 serum levels are associated with poorer cognitive performance. A longitudinal study [42] has linked PDCI to reduced levels of growth factors in cerebrospinal fluid and plasma, such as brain-derived neurotrophic factor (BDNF) and epidermal growth factor (EGF). Huang et al. confirmed [43] that the concentration of BDNF in plasma in depressed patients was reduced compared with non-depressed patients, and the concentration of BDNF was also found to be reduced in SN and hippocampus in PD patients compared with non-PD patients.

5.3. Homocysteine

The current hypothesis that Hcy levels affect PD progression is mainly that elevated Hcye levels can produce pro-oxidative activity, leading to the production of an unstable neurotoxic product - cysteine sulfinic acid, which acts as an N-methyl-D-aspartate (NMDA) receptor agonist, has neurotoxic effects on DA, and may be involved in neurodegenerative mechanisms such as excitotoxicity, oxidative stress, calcium accumulation and apoptosis. Guo Chang et al. [44] showed that the plasma homocystic level of patients in the PD group was higher than that in the control group; In patients with PD with different homocystic levels, those with high homocystic levels scored lower than those with normal homocystic levels. Shen Genming et al. [45] used memantine in the treatment of patients with DPD and CI, believing that the drug improves patients' depression and cognition by promoting the release of DA, antagonizing NMDA, and inhibiting its toxicity. It is speculated that plasma homocystic levels can be used as biomarkers for predicting PDCI and DPD, and lowering homocystic levels is expected to treat and improve neurological function in PD patients.

ISSN: 2688-8653

5.4. Uric acid

UA is both an antioxidant and an iron chelator with neuroprotective effects, and the significant correlation between UA levels and the severity of DA lesions in the caudate nucleus, putamen, and striatum also confirms that serum UA levels are inversely correlated with the progression of PD [46]. Qiu Ju et al. [47] believed that the serum UA level of PD patients was not significantly related to their motor symptoms, but was negatively correlated with depression and anxiety, and positively correlated with CI. Ye Ming et al. [48] found that the lower the serum UA level of PD patients, the lower the scale score, that is, the UA level was positively correlated with cognitive function. Zhu et al. [49] believe that a decrease in serum UA levels in DPD patients and PDCI patients may be related to free radical formation and oxidative stress, thereby increasing cell death in the SN dense part. These findings suggest that monitoring serum UA levels may be a potential biomarker or therapeutic strategy for PD. However, serum UA levels can be used to assess the possibility of non-motor symptoms of PD with CI, anxiety, depression, apathy, and dysphagia, and larger clinical and preclinical studies are needed to further explore the underlying mechanisms of changes in serum UA levels in PD patients.

5.5. Gene

A systematic review analysis of the literature confirmed [50] that the variants rs76763715 and rs421016 in glucocerebrosidase gene (GBA) on inherited gene expression were not only associated with more severe cognitive impairment in PD patients, but also significantly associated with the onset of DPD. The minor alleles of the GBA variants rs76763715 and rs421016 cause glucocerebrosidase (GCase) to misfold, which may lead to loss of neurological function. In addition, GSase deficiency can lead to impaired autophagy, mitochondrial dysfunction, and accumulation of α-synuclein oligomers α that disrupt misfolded GCases and set off a vicious cycle leading to neurodegeneration and CI in PD patients carrying GBA variants. Decreased GCase activity and expression levels were observed in SN in PD patients, which also confirmed that GBA variant carriers were associated with the risk of PD.

6. Therapy

Pramipexole, one of the commonly used drugs for the clinical treatment of DPD, has the latest research [51] that pramipexole can alleviate cognitive impairment in PD patients by protecting DA neurons and midbrain SN while fighting depression, but this conclusion still needs to be supported by further large-scale studies. In addition, an experimental study [52] showed that vortioxetine, as a multimodal 5-HT antidepressant, significantly reduced rotenone-induced neurodegeneration, repaired the inflammatory response to injury, and affected neurotransmitter levels in brain tissue, thereby reducing depressive-like behavior and improving motor and cognitive dysfunction. Other researchers believe [53] that cognitive behavioral therapy (CBT), exercise and other adjuvant therapies can alleviate depressive symptoms and improve multiple cognitive domains such as attention, working memory and EF ability to a certain extent.

7. Conclusion

In summary, although the mechanism of correlation between depression and cognitive impairment is still unclear, DPD and PDCI have a common pathological mechanism, of which DA is mainly impaired, and other neurotransmitters such as NE, 5-HT, etc. also interact with DA, thereby aggravating depression and cognitive impairment in PD patients. The role of autoimmunity and inflammatory response has also been gradually emphasized, among which the brain-gut axis theory emphasizes the relationship between gastrointestinal inflammation and brain nerves. At the same time, depression mainly affects attention and memory in

ISSN: 2688-8653

cognitive function, and also accelerates the development of PD-MCI to PDD. There is no specific drug to reverse DPD and PDCI in clinical practice, but recently through continuous research on the efficacy of acupuncture and drug combination, more convenient treatment options with less side effects have been provided for clinical practice. In view of the high disability rate and high mortality caused by depression and cognitive decline to PD patients, more and more in-depth clinical studies are still needed in the future to explore the biomarkers related to the two, so as to better predict or monitor the neurological damage of PD patients, which also means that more possible therapeutic targets and interventions can be used for clinical reference.

References

[1] Kalia LV, Lang AE. Parkinson's disease. Lancet. 2015 Aug 29;386(9996):896-912.

[2] Tysnes OB, Storstein A. Epidemiology of Parkinson's disease. J Neural Transm (Vienna). 2017 Aug;124(8):901-905.

[3] Beitz JM. Parkinson's disease: a review. Front Biosci (Schol Ed). 2014 Jan 1;6(1):65-74.

[4] Munhoz RP, Moro A, Silveira-Moriyama L, et al. Non-motor signs in Parkinson's disease:a review[J]. Arq Neuropsiquiatr, 2015, 73(5): 454-462.

[5] Marsh L. Depression and Parkinson's disease: current knowledge. Curr Neurol Neurosci Rep. 2013 Dec;13(12):409.

[6] Gonzalez-Latapi P, Bayram E, Litvan I, et al. Cognitive Impairment in Parkinson's Disease: Epidemiology, Clinical Profile, Protective and Risk Factors. Behav Sci (Basel). 2021 May 13;11(5):74.

[7] YANG Shiyu, WANG Yi, JIN Yanfei, et al. The interaction between depression and mild cognitive impairment and the research progress of interventions[J].Chinese Community Physician,2022,38(01):6-8.

[8] Laux G. Parkinson and depression: review and outlook. J Neural Transm (Vienna). 2022 Jan 4.

[9] Kitamura S, Nagayama H. [Depression in Parkinson's disease]. Seishin Shinkeigaku Zasshi. 2013;115(11):1135-41.

[10] Timmer MHM, van Beek MHCT, Bloem BR, et al. What a neurologist should know about depression in Parkinson's disease. Pract Neurol. 2017 Oct;17(5):359-368.

[11] Latoo J, Mistry M, Dunne FJ. Depression in Parkinson's disease: diagnosis and management. Br J Hosp Med (Lond). 2012 Jun;73(6):331-4.

[12] Williams JR, Hirsch ES, Anderson K, et al. A comparison of nine scales to detect depression in Parkinson disease: which scale to use? Neurology. 2012 Mar 27;78(13):998-1006.

[13] Goodarzi Z, Mrklas KJ, Roberts DJ,et al. Detecting depression in Parkinson disease: A systematic review and meta-analysis. Neurology. 2016 Jul 26;87(4):426-37.

[14] Biemiller R, Richard IH. Managing depression in Parkinson's patients: risk factors and clinical pearls. Neurodegener Dis Manag. 2014;4(4):329-36.

[15] FAN Shaokai, LI Binghan, HAN Boya, et al. Pathogenesis and treatment progress of Parkinson's disease with depression[J].Hainan Medical Journal,2021,32(06):770-773.

[16] Wilson H, de Natale ER, Politis M. Nucleus basalis of Meynert degeneration predicts cognitive impairment in Parkinson's disease. Handb Clin Neurol. 2021;179:189-205.

[17] Roheger M, Kalbe E, Liepelt-Scarfone I. Progression of Cognitive Decline in Parkinson's Disease. J Parkinsons Dis. 2018;8(2):183-193.

[18] Wang YQ, Tang BS, Yan XX, et al. A neurophysiological profile in Parkinson's disease with mild cognitive impairment and dementia in China. J Clin Neurosci. 2015 Jun;22(6):981-5.

[19] Pedersen KF, Larsen JP, Tysnes O-B, et al. Prognosis of mild cognitive impairment in Early Parkinson disease: the Norwegian ParkWest study. JAMA Neurol 2013;70(5):580–586.

[20] Aarsland D, Creese B, Politis M, et al. Cognitive decline in Parkinson disease. Nat Rev Neurol. 2017 Apr;13(4):217-231.

ISSN: 2688-8653

[21] Sun C, Armstrong MJ. Treatment of Parkinson's Disease with Cognitive Impairment: Current Approaches and Future Directions. Behav Sci (Basel). 2021 Apr 17;11(4):54.

[22] Baiano C, Barone P, Trojano L, et al. Prevalence and clinical aspects of mild cognitive impairment in Parkinson's disease: A meta-analysis. Mov Disord. 2020 Jan;35(1):45-54.

[23] Gonzalez-Latapi P, Bayram E, Litvan I, Marras C. Cognitive Impairment in Parkinson's Disease: Epidemiology, Clinical Profile, Protective and Risk Factors. Behav Sci (Basel). 2021 May 13;11(5):74.

[24] Sinaeefar MJ, Saadat P, Hamidia A, et al. Evaluation of the cognitive impairments and depressive symptoms in patients with Parkinson's disease: A case-control study from Iran. Clin Neurol Neurosurg. 2021 Apr;203:106549.

[25] Park, J. H., Lee, S. H., Kim, Y., et al. (2020). Depressive symptoms are associated with worse cognitive prognosis in patients with newly diagnosed idiopathic Parkinson disease. Psychogeriatrics. Doi:10.1111/psyg.12601.

[26] Forbes, E., Tropea, T. F., Mantri, S., et al. (2021). Modifiable Comorbidities Associated with Cognitive Decline in Parkinson's Disease. Movement Disorders Clinical Practice, 8(2), 254–263.

[27] Jones JD, Kurniadi NE, Kuhn TP, et al. Depressive symptoms precede cognitive impairment in de novo Parkinson's disease patients: Analysis of the PPMI cohort. Neuropsychology. 2019 Nov;33(8):1111-1120.

[28] WU Aiqin,CHEN Hongquan. The effect of depression associated with early Parkinson's disease on cognitive function[J].Practical Geriatrics,2017,31(10):917-920.

[29] CHEN Jing, XU Pengfei, ZHOU Peiran, et al. Association between depression and cognitive function in patients with Parkinson's disease and depression[J].Journal of Guizhou Medical University,2021,46(12):1409-1413+1420.

[30] Wen MC, Chan LL, Tan LC, et al. Depression, anxiety, and apathy in Parkinson's disease: insights from neuroimaging studies. Eur J Neurol. 2016 Jun;23(6):1001-19.

[31] Timmer MHM, van Beek MHCT, Bloem BR, et al. What a neurologist should know about depression in Parkinson's disease. Pract Neurol. 2017 Oct;17(5):359-368.

[32] Speranza L, di Porzio U, Viggiano D, et al. Dopamine: The Neuromodulator of Long-Term Synaptic Plasticity, Reward and Movement Control. Cells. 2021 Mar 26;10(4):735.

[33] WEI Ke. Correlation between human serum vitamin D and 5-HT, DA levels and Parkinson's disease with depression[D].Hainan Medical College,2020.DOI:10.27952/d:cnki.ghnyx.2020.000080.

[34] JIANG Lulu. The role and mechanism of norepinephrine in the occurrence and development of Parkinson's disease[D].Shandong University,2016.

[35] Del Tredici, K.,Braak, H. (2012). Dysfunction of the locus coeruleus-norepinephrine system and related circuitry in Parkinson's disease-related dementia. Journal of Neurology, Neurosurgery & Psychiatry, 84(7), 774–783.

[36] ZHU Wenming, WANG Jihong, ZHU Li Li, et al. Changes in serum serotonin, epinephrine and inflammatory factor levels in patients with Parkinson's disease complicated by depression and their relationship with cognitive dysfunction[J].International Journal of Psychiatry, 2016,43 (06):981-984+988.

[37] SHAO Ziqiang, WANG Guoxiang, JIAO Jinsong, et al. Changes in platelet serotonin levels in patients with Parkinson's disease and its relationship with depression and cognitive dysfunction[J].Journal of Clinical Neurology,2011,24(04):264-266.

[38] Jakova E, Moutaoufik MT, Lee JS, et al. Adenosine A1 receptor ligands bind to α-synuclein: implications for α-synuclein misfolding and α-synucleinopathy in Parkinson's disease. Transl Neurodegener. 2022 Feb 10;11(1):9.

[39] Jenner P, Mori A, Kanda T. Can adenosine A2A receptor antagonists be used to treat cognitive impairment, depression or excessive sleepiness in Parkinson's disease? Parkinsonism Relat Disord. 2020 Nov;80 Suppl 1:S28-S36.

[40] De Virgilio A, Greco A, Fabbrini G, et al. Parkinson's disease: Autoimmunity and neuroinflammation. Autoimmun Rev. 2016 Oct;15(10):1005-11.

ISSN: 2688-8653

[41] Pessoa Rocha N, Reis HJ, Vanden Berghe P,et al. Depression and cognitive impairment in Parkinson's disease: a role for inflammation and immunomodulation? Neuroimmunomodulation. 2014;21(2-3):88-94.

[42] Pellecchia MT, Santangelo G, Picillo M.et al. Serum epidermal growth factor predicts cognitive functions in early, drug-naive Parkinson's disease patients. J Neurol. 2013 Feb; 260(2):438-44.

[43] Huang Y, Huang C, Zhang Q, et al. Serum BDNF discriminates Parkinson's disease patients with depression from without depression and reflect motor severity and gender differences. J Neurol. 2021 Apr;268(4):1411-1418.

[44] GUO Chang,SHEN Huinan,SUN Yimeng,WANG Dongyu. Association between blood lipids and homocysteine and cognitive impairment in Parkinson's disease[J].Clinical Meta,2022,37(02):128-132.

[45] SHEN Genming,DING Xiaojie,JIANG Jianping,SHEN Juanhui. The effect of memantine on patients with Parkinson's disease complicated with cognitive dysfunction with depressive episodes[J].Modern Practical Medicine,2021,33(08):1094-1096.

[46] Tana C, Ticinesi A, Prati B, et al. Uric Acid and Cognitive Function in Older Individuals. Nutrients. 2018 Jul 27;10(8):975.

[47] QIU Ju,DU Jing,RAO Jing,GAO Zongliang. Correlation between serum uric acid level and clinical symptoms in patients with Parkinson's disease[J].Anhui Medical Journal,2014,35(08):1061-1064.

[48] YE Ming,XU Juanjuan,XIE Jing,SHI Peng,ZHANG Lina,LIU Xiaolin. Correlation analysis between serum cystatin C and uric acid levels and cognitive dysfunction in Parkinson's disease[J].Journal of Bengbu Medical College,2020,45(02):185-188.

[49] ZHU Yonghui,LIU Qian,XU Li,ZHENG Mao. Correlation between blood uric acid level and clinical stage, depression and cognitive impairment of Parkinson's disease in the elderly[J].Medical Theory & Practice,2020,33(06):866-868.

[50] D'Souza T, Rajkumar AP. Systematic review of genetic variants associated with cognitive impairment and depressive symptoms in Parkinson's disease. Acta Neuropsychiatr. 2020 Feb;32(1):10-22.

[51] Li ming. Clinical effect of pramipexole in the treatment of Parkinson's disease and depression and its effect on cognitive function[J].Clinical Medical Research and Practice,2022,7(03):46-48.

[52] Nemutlu Samur D, Akçay G, Yıldırım S, et al. Vortioxetine ameliorates motor and cognitive impairments in the rotenone-induced Parkinson's disease via targeting TLR-2 mediated neuroinflammation. Neuropharmacology. 2022 May 1;208:108977.

[53] Dauwan M, Begemann MJH, Slot MIE, et al. Physical exercise improves quality of life, depressive symptoms, and cognition across chronic brain disorders: a transdiagnostic systematic review and meta-analysis of randomized controlled trials. J Neurol. 2021 Apr;268(4):1222-1246.