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Review Article

Inflammation on the crossword of Parkinson's disease and COVID-19

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ABSTRACT

Worldwide pandemic of COVID-19 has resulted in various physiological manifestations mainly affecting the respiratory system and also the nervous system. Inflammation, a hallmark symptom of diseases links both COVID-19 and neurodegenerative disorders. COVID-19 infection resulted in immune responses like cytokine and chemokine production, and even cytokine storms (in severe cases), which lead to inflammation. Parkinson's Disease (PD), characterised by motor difficulties is mainly due to α -synuclein aggregates and the disease is known to have dual instigations. In one way the central inflammation caused due to tissue injury, glial cell dysfunction and proinflammatory molecule production, resulting in Blood Brain Barrier leakage and in another way peripheral inflammation occurs due to altered gut microbiome after pathogen attack, producing inflammatory mediators. Inflammation being a potential threat for onset and progression of PD is the major concern of this article. Immediate effect of COVID-19 might be respiratory ailment and hypoxia might contribute to inflammation but the long-lasting effects are uncertain which might increase neurodegenerative diseases in future. Anti-inflammatory therapeutic interventions have already shown varied results for COVID-19 infections of various stages but its impact on PD is yet to be studied. Here, we have elucidated the role of inflammation in the pathophysiology of PD and developing new therapeutic approach by targeting the inflammatory cascade.

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1. Introduction

The year 2019 saw the advent of novel corona virus named COVID-19 affecting 229 countries across the world.¹ Like other related members of coronavirus family, its primary characteristics include fever, cough and respiratory illness, however there are other multi-organ manifestations,² due to the various ways of entry that includes the gastrointestinal tract.³ Major consequences of COVID-19 infection include renal injury, thrombosis, coagulopathy and post-infection multi-system inflammation in children.^{4,5} COVID-19 affected patients were seen to develop neurological issues like encephalopathies, ischemic strokes, inflammatory central nervous system

syndromes, disorders of peripheral nervous system.⁶ Pathophysiological and environmental factors (sedentary lifestyle, reduced physical activity, reduced sunlight exposure and social distancing) have contributed towards development of mental and cellular stress giving rise to a series of neurological defects including neurodegenerative and neuroinflammatory diseases (e.g., Parkinson's Disease (PD), Alzheimer's Disease (AD)).

PD ranks second in the list of neurodegenerative disease after AD affecting 9 million people worldwide.⁷ Motor activity is disrupted in PD patients which is mainly due to death of dopaminergic neurons projecting from substantia nigra but the non-motor aspects of PD including insomnia, constipation, reduced smell perception, can be attributed to the serotonergic and cholinergic tracts along with dopaminergic tracts projecting from extra-

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nigral areas.⁸ Considering PD as a geriatric problem due to late appearance of symptoms, yet onset of the disease is much earlier but the actual cause is indefinite. The major molecular mechanisms include misfolding or aggregation of α -synuclein, mitochondrial dysfunction, improper protein clearance via ubiquitin-proteasome and autophagy-lysosomal systems malfunctioning, oxidative stress and neuroinflammation.⁹

Genetic and environmental factors regulate disease cascade.¹⁰ Apart from the genetic causes (mutation or genetic polymorphism of PARK and other linked genes like LRRK2, PINK, VDR), environmental factors include exposure to pesticides and toxins, smoking, traumatic lesions and bacterial or viral infection can lead to the onset and aggravation of PD¹¹ which are closely linked to inflammation.

2. Inflammation

Inflammation is a highly regulated and response elicited upon tissue injury or pathogenic invasion, which protects the host from the pathogens and foster tissue repairment. Inflammation often results in changes in cellular metabolic energy. Pro-inflammatory molecules like interleukin-6 (IL-6), plasma C-reactive protein (CRP), plasminogen activator inhibitor-1, tumour necrosis factor- α (TNF- α), or monocyte chemoattractant protein-1, are released at the inflammation site which activates immune cells increasing their energy consumption leading to local hypoxia and anaerobic metabolism. Resulting mitochondrial dysfunction leads to production of free radicals and prolonged imbalance causes oxidative stress and ultimately oxidative damage.¹²

2.1. Inflammation and parkinson's disease

Parkinson-like symptoms were observed in influenza virus (encephalitis lethargica) affected people and since then inflammatory manifestations were targeted for study and various other viral pathogenic association with PD onset have been established.¹³ As postulated by Braak et al, 2003, pathogenic entry and its basal ganglia invasion is "dual-hit", one through the nasal tract and other through enteric plexuses and preganglionic vagal fibres invading the intestinal mucosa, eventually initiating a cascade of neuroinflammatory and neurodegenerative processes in the nigrostriatal tract.^{14,15} Some viral proteins like Herpes simplex virus-1 (HSV-1) and Ebola virus structurally mimic α -synuclein molecule and promotes α -synuclein aggregation and intra-cellular accumulation in form of Lewy Bodies, which are the anatomical markers of PD.¹⁶ After viral infection, in the enteric nervous system α -synuclein attracts monocytes and neutrophils which is a clear indication of inflammation in PD pathogenesis.¹⁷

Blood Brain Barrier (BBB) separates central nervous system (CNS) and peripheral immune system. However,

PAMPs or Pathogen-Associated Molecular Patterns and DAMPs or Damage-Associated Molecular Patterns elicit immune responses in the CNS. Glial cells (microglia and astroglia) release neurotrophic factor and exhibit neuroprotective functions against stress mediators maintaining CNS homeostasis but PAMPs and DAMPs like secretions from dead neurons or aggregated proteins may activate glial cells leading to prolonged neuroinflammation.¹⁸ In PD patients' CSF and serum cytokines like IL-6, IL-2, TNF α , IL-1 β , IFN γ , and CD4+ lymphocyte counts were elevated.¹⁹

Human and animal model studies have proven link between inflammation and PD. Although the direct cause is indistinct, yet misfolded α -synuclein might be a direct trigger. Along with astrogliosis and microgliosis in PD patients, peripheral inflammation and genetic intervention also contribute towards establishing the link chronic inflammation and PD progression.

2.1.1. Role of microglia and astrocytes

Microglia aids brain development and functioning as resident macrophages of CNS, maintaining CNS homeostasis under normal physiological conditions by secreting neurotrophic factors, neuron repairing and remodelling and synaptic pruning.¹⁸ Upon activation by tissue injury or inflammatory stimuli, they polarise towards proinflammatory M1 phenotype (classical) or the protective M2 phenotype.²⁰ DAMPs released from degrading neurons like neuromelanin, m-calpain, proinflammatory mediators, misfolded or aggregated proteins (α -Syn) and Toll-like receptors (TLRs) signalling prefers the M1 phenotype,²¹ a large and amoeboid cell and upregulated major histocompatibility complex (MHC) I and II molecules with augmented proinflammatory mediators (cytokines, chemokines and bioactive lipids) production causing neuronal damage. Thus, the BBB permeability is altered infiltrating brain with circulating leukocytes, boosting local inflammatory response.²² TNF α interacts with TNFR1 activating caspases 1 and 3 causing apoptosis.²³ TNF α hinders c-Rel (neuroprotective NF- κ B isoform inhibits SN-dopaminergic neuron apoptosis).²⁴ NF- κ B/c-Rel deficiency causes PD-like prodromal symptoms and progressive pathology in mice. Presence of CXCR4 (chemokine receptor) and CXCL12 (ligand) in PD patients, justifies apoptotic death of neurons via CXCR4-CXCL12 signalling activating caspase 3.²⁵

They also induce gene expression of the NADPH oxidase system, reactive nitrogen (nNOS and eNOS, not iNOS) and oxygen species (ROS) production in humans and antimicrobial activity to combat chronic inflammation.²⁶

Recurrently activated microglia initiate a feed-forward cycle of neuroinflammation and neurodegeneration by secreting proinflammatory cytokines producing damaged neurons and further activation of microglia.

Most abundant astrocytes form the backbone of neurovascular unit by directly linking neurons with blood vessels. Functionally astrocytes provide lactate for mitochondrial respiration, maintain BBB and its permeability and regulates cerebral blood flow.²⁷ A1 Astrocyte maintains proper synaptic functions and phagocytosis of neuronal debris or damaged synapse but secrete IL-1 α , TNF α , C1q and some unknown neurotoxic factor(s) (M1 analogy), fostering neuron and oligodendrocyte death. A2 astrocytes provide neuroprotection upon ischemia or other neurotrophic factor(s). A1 astrocytes are significantly high in PD patients. Its activation is mostly through M1 microglia intervention.^{28,29}

Among 17 monogenic genes of PD development, 8 (PARK7, SNCA, LRRK2, PINK1, PARK2, GBA, PLA2G6, and ATP13A2) are expressed in astrocytes,³⁰ including some genes triggering inflammation. DJ1 protein encoding PARK7 gene is involved in signalling, receptor trafficking and also endocytosis. Its disruption or deficiency causes excitotoxicity and compromised TLR3/4-mediated endocytosis leading to proinflammatory cytokine production.^{31,32}

α -Synuclein aggregates were found in neurons as well as astrocytes and evidences show transmission of these aggregates from neurons to astrocytes³³ resulting in amplified ROS production and intercellular adhesion molecule 1 (ICAM1) expression and increased inflammatory cytokine production.³⁴ Activated senescent astrocytes produce TNF α which bind to TNFR1 and 2 (specific receptors expressed by dopaminergic neurons) and activate proapoptotic machinery.²⁹

2.1.2. Inflammation of brain endothelium and Permeability of BBB

Brain endothelium, another fundamental unit of neurovascular unit, maintains CNS homeostasis including leucocyte adhesion, mechano-transduction, vascular permeability regulation and impeding brain damage. Brain endothelium activity is altered by inflammatory molecule production by microglia and astrocytes. Endothelial cells themselves express TLR and elicit inflammatory responses to PAMPs and DAMPs, releasing cytokines, chemokines and adhesion molecule, ultimately causing endothelial dysfunction, blood cells intruding brain microvasculature through adhesion molecules.³⁵ Adhesion molecule VCAM1 was elevated in PD patients of various severity stages indicating correlation between blood-brain connections and cell traffic.³⁶ Neuroinflammation related abnormal vasculature in PD is accompanied by BBB leakage.³⁷ Figure 1 shows the detailed events in central inflammation.

Cytokines like TNF α , IFN- γ or IL1 β were experimentally found to decrease trans-endothelial

electrical resistance, marking inflammation the prime culprit for altering BBB permeability³⁸ although cell death was not associated with BBB leakage decreased in TNF α knockout mice reducing microglial activation and less expression of inflammatory mediators but no reduction in neuronal loss.³⁹ Vascular defects in PD should be stated after considering the age and comorbidity of the patient.⁴⁰

2.1.3. Peripheral inflammation and PD prognosis

Altered neurovascular unit activates both innate as well as adaptive immune responses in PD patients. Oxidative modification of typical PD-associated protein (i.e., nitrated α -Synuclein) generates unique antigenic epitopes which commences responses of peripheral CD4+ and CD8+ T cell and nigral neuronal degeneration.⁴¹ Prolonged overexpression of IL-1 β in the SN can prompt major attributes of PD like progressive dopaminergic neuronal death, dyskinesia and ultimately akinesia and activation of glial cell.⁴² As shown in Figure 1, peripheral inflammation triggers BBB or Vagus nerve stimulation, converting “primer” microglia into “active” microglia for sustaining neurodegeneration. The strongly interconnected enteric nervous system and immune system is highly influenced by the gut microbiota and might regulate “gut-brain-axis”. Dysregulation of this axis explains the gut disturbances in prodromal stages of PD also increasing the vulnerability of dopaminergic neurons in inflamed gut condition.⁴³ Altered gut microbiome favours α -synuclein aggregation and causes peripheral inflammation resulting in increased cytokine levels. Studies have shown that oxidative markers like SOD, TNF-a and IL-6 derived from peripheral inflammation increased with PD progression.⁴⁴

2.2. Inflammation and Covid

A number of recent studies have come up with evidences suggesting COVID-19 as immune-related disorder as failure of effective immune responses during initial stages of viral infection is linked to worse disease outcomes (systemic and tissue damage). Effective innate and adaptive immunity against viruses lead to secretion of different pro-inflammatory cytokines.⁴⁵ Activated T cell subsets incumber viral replication and finally restrain the virus by resolving inflammation. On the contrary, SARS-CoV-2 leads to tissue injury by stimulating excessive secretion of pro-inflammatory cytokines. Recruitment of pro-inflammatory cells by the virus including granulocytes and macrophages also instigate tissue injury. COVID-19 patients are shown to have an altered level of various cytokines and chemokines during mild to severe stage of the disease like the level of IL-6, IL-1 β , IL-8, IL-10, TNF- α , IFN- γ , and G-CSF are increased.⁴⁶

Particularly, abnormal levels of IL-2 and IL-6 in plasma is correlated to aggravated lung injury. IL-6 significantly contribute in cytokine storm in mild and severe SARS-

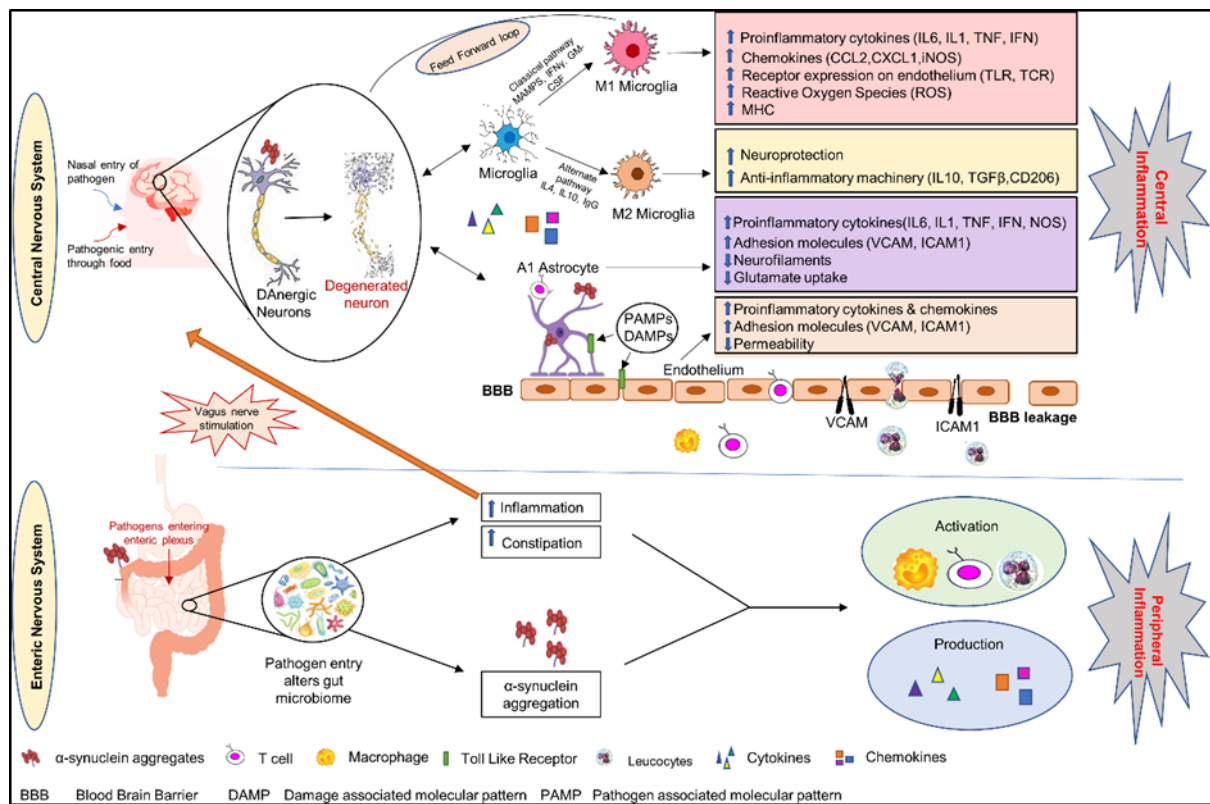


Fig. 1: Central and peripheral inflammation contributing to Parkinson’s disease. Synuclein aggregation causes neurodegeneration which causes activation of microglia into proinflammatory M1 and neuroprotective M2 phenotype, A1 Astrocyte activation along with PAMPs and DAMPs which also activate endothelium TLRs, all resulting in production of proinflammatory molecules, ROS, NOS, adhesion molecules causing BBB leakage. Oral and nasalpathogen entry alter gut microbiome causing synuclein aggregation and inflammatory responses which further affect CNS via Vagus nerve stimulation

CoV-2 infected patients. Upon SARS-CoV-2 infection, active pathogenic T cell secrete granulocyte-macrophage colony stimulating factor (GM-CSF) and IL-6. Additionally, CD14+ and CD16+ inflammatory monocytes are activated as a result of GM-CSF secretion in turn secreting more IL-6.⁴⁷

C-Reactive Protein is a systemic biomarker produced as a result of acute-phase inflammation, pathogenic infection and tissue damage.⁴⁸ Although there is no significant difference in CRP levels between severe and non-severe patients, yet CRP levels have been found to be elevated in case of severe patients.⁴⁹ ESR (erythrocyte sedimentation rate), a non-specific inflammatory marker majorly reflects changes in types of plasma protein.⁵⁰ ESR levels were also elevated in sever patients probably due to high inflammation in severe patients. Age might also play a role in elderly severe patients as ESR levels increase with age.⁵¹

Treatment of COVID-19 is pretty challenging yet several approaches are being undertaken showing significant results. A deep understanding of immune responses, especially T cells is very important for COVID19 treatment as it elicits protective role in early infection stage

but might later lead to fatal comorbidities. In case of severe cases, SARS-CoV-2 infection can be controlled by targeting inflammation and prevent deterioration of the secondary complications. Therapeutic intervention should be strategically planned because blocking proinflammatory cytokines in mildly symptomatic patients would be detrimental due to deficient immune response and reduced viral clearance whereas late therapeutic interventions to regress T-cell exhaustion and improving hyperinflammatory responses for severely affected COVID-19 patients might elute better outcomes.

2.3. Covid and parkinson’s disease

1. Coronaviruses can enter the nasal cavity and enter the CNS causing neuronal death.⁵²
2. Hyposmia is a characteristic symptom of COVID19 infection⁵³ which is also a prodromal feature of PD.⁵⁴
3. Antibodies against other coronaviruses have been found in elevated levels in CSF of PD patients suggesting viral infection in PD pathogenesis.⁵⁵
4. Expression of ACE2 is found in various neural regions and interferon activation of ACE2 protein need to

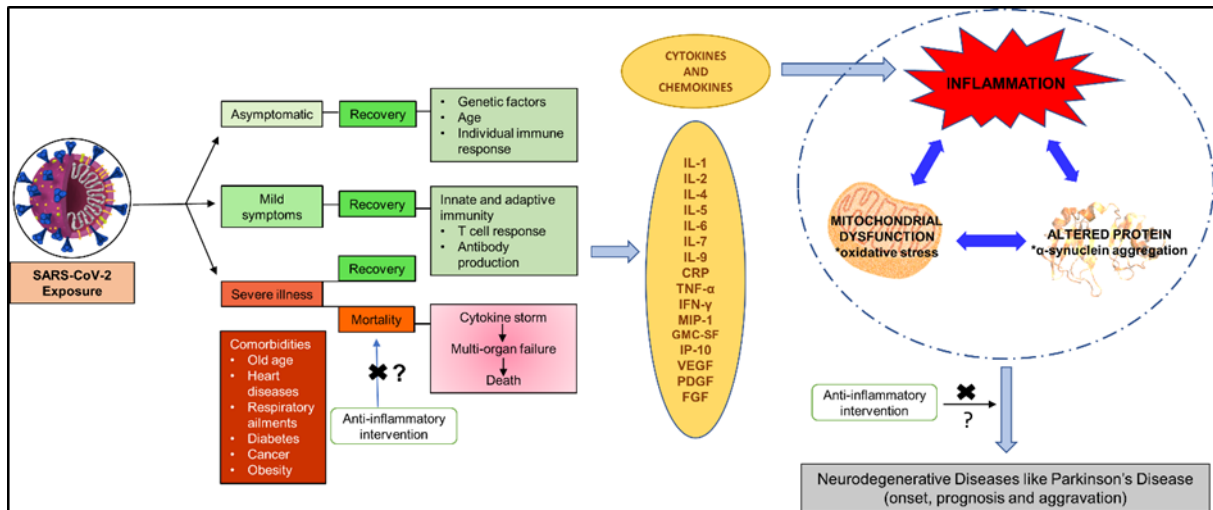


Fig. 2: COVID-19 infection and resultant inflammation instigating neurodegenerative diseases like Parkinson's disease. COVID-19 infection causes release of cytokines and chemokines which cause inflammation and along with mitochondrial dysfunction causes aggregation of protein leading to PD. Anti-inflammatory therapies have shown varied impact on COVID-19 patients and its effectivity against PD prognosis is undecided

be examined in subjects with CNS inflammation or encephalitis.⁵⁶

- The angiotensin system implicated in COVID-19 pathogenesis is important in neuroinflammatory and neurodegenerative mechanisms witnessed in PD.⁵⁷
- SARS-CoV-2 proteins interact with human proteins involved in biological systems disrupting protein homeostasis leading to misfolding and aggregation of proteins.⁵⁸
- Cytokines activate innate immune cells like T cells and microglia which might destroy astrocytes, neurons, vascular cells and also cause peripheral inflammation.⁵⁹ Increased pro-inflammatory cytokines (e.g., $TNF\alpha$ and $IL-1\beta$) increase PD incidence, whereas non-steroidal anti-inflammatory drugs (NSAIDs) and anti- $TNF\beta$ therapy might minimise the risk.⁶⁰ Currently, anti- $TNF\alpha$ medication is under investigation for COVID-19.

2.4. Vitamin D as a therapeutic agent against inflammation

Parkinson's disease and COVID-19 progression share some common biochemical pathways including oxidative stress, inflammation, and protein aggregation.⁶¹ Studies show that Vitamin D might act as an immunosuppressant by inhibiting Cytokine Release Syndrome in COVID-19 and it might also prevent loss of neural sensation in COVID-19 by stimulating expression of neurotrophins like Nerve Growth Factor.⁶² Deficiency or insufficient 25-hydroxyvitamin D and reduced exposure to sunlight were significantly associated with an increased risk of Parkinson's disease but vitamin D supplements did not yield improving motor function for

patients with Parkinson's disease.⁶³

3. Discussion

Inflammatory cytokine like IL-6 was found to be 2.5 times more in COVID-19 affected people.⁶⁴ Even though the main cause of PD onset or α -synuclein aggregation is unknown, yet inflammation and tissue injury seem to initiate the activation of innate and adaptive immune cells. The gut microbiota has an impact on neurodevelopment, behaviour modulation, and contributes to neurological disorders. Studies in mice have shown that when colonization of α -Synuclein-overexpressing mice were treated with PD-affected patient's microbiome then they exhibit enhanced motor disability than treated with microbiome from healthy individuals. It revealed the role of gut bacteria in regulating movement disorders and thus altered gut microbiome is a threat for PD.⁶⁵

COVID-19 has resulted in several neurological and neuropsychiatric manifestations with clinical manifestations of central as well as peripheral nervous system⁶⁶ with inflammation playing a central role. Inflammatory cytokine, IL-6 have been found significantly high in COVID-19 patients and elevated CRP levels in serum is attributed to Macrophage Activation Syndrome, generally absent in other viral infections.⁶⁷ In PD, proinflammatory biomarker levels were correlated with severity of disease with increased levels was correlated with worsened motor function and increased cognitive impairment, indicating an association between inflammation and greater aggressive disease progression.⁶⁸

Inflammation is a key factor which could be triggered by COVID-19 infection which might pose a potent threat for

PD in all stages, from initiation to slow prognosis and also in augmentation of symptoms and difficulties associated with PD, calls for further detailed research. Figure 2 is a diagrammatic representation of projected future threat for neurodegenerative diseases like PD, AD, etc.

Inflammation is a normal coping up strategy of short-term immune response to trauma, illness, and stress. However, with drastically changing life style in new-normal of Covid pandemic era especially for home-bound senior citizens inflammation is becoming long-term and chronic. Along with other necessary therapies personalised dietary intervention emphasising on vitamin D could be a promising way to ameliorate the threats of stress and inflammation.⁶⁹

4. Conclusion

Anti-inflammatory therapies are studied against inflammatory diseases including PD,⁷⁰ but natural or food supplements with minimal side effects, which might be helpful to curb or prevent inflammation thus prevent or delay PD onset or curb disease progression of PD and also prevent the onset of unforeseen diseases as aftermath of COVID-19 pandemic, are yet to be established. Vitamin D has been used as a medication against COVID-19 infection and also vitamin D is found deficient in PD patients. It is an area of further in-silico and in-vitro research to analyse the effect of Vitamin D on PD patients and also to find out if there are any genetic anomalies like polymorphism as to why vitamin D supplementation are not improving motor disabilities in all cases.

5. Abbreviations

AD: Alzheimer's disease; BBB: Blood brain barrier; CNS: Central nervous system; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; GM-CSF: Granulocyte-macrophage colony stimulating factor; ICAM1: Intercellular adhesion molecule 1; IL-6: Interleukin-6; NSAIDs: Non-steroidal anti-inflammatory drugs; PD: Parkinson's disease; TNF- α : Tumour necrosis factor- α

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7. Author's Contributions

Randrita is currently working with genetics and Parkinson's Disease (PD) and has written the manuscript and formed the figures of this article. Barnali had designed the concept of this article and provided her expertise for all aspects of its review and editing of the manuscript.

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