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Mini Review

Pathogenesis of Post-COVID-19 Parkinsonism and Parkinson's Disease

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Abstract

After Alzheimer's disease, Parkinson's disease (PD) is the most common neurological condition worldwide. The hallmarks of Parkinson's disease (PD) are misfolded alpha-synuclein aggregation and dopaminergic neuron degeneration in the substantia nigra pars compacta, along with both motor and non-motor symptoms. A post-infection parkinsonian phenotype's presence has been connected to several viruses. As a result of the emergence of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, the 2019 coronavirus disease (COVID-19), which initially manifested as novel pneumonia, has developed into a complex syndrome with a variety of clinical manifestations, including subtle and potentially long-lasting neurological sequelae. Exosomes are extracellular nanovesicles that play essential roles in intercellular communication in pathological situations. They carry a complex cargo of active biomolecules. Exosomes are a dependable method of misfolded protein transfer that aid in the pathophysiology and diagnosis of Parkinson's disease. Here, we review current research that suggests PD and SARS-CoV-2 infection share several clinical symptoms as well as inflammatory and molecular mechanisms. We continue to speculate that these commonalities may be represented in exosomal cargo that is altered by the virus in connection to the severity of the sickness. The SARS-CoV-2-related exosomal cargo moves from the brain to the periphery and carries SARS-CoV-2 RNA, viral proteins, inflammatory mediators, and modified host proteins that may act as promoters of neurodegenerative and neuroinflammatory cascades and eventually result in the development of parkinsonism and PD.

Keywords: Parkinson's disease • SARS-CoV-2 • Exosomes • Neuroinflammation • Inflammation • Parkinsonism • Alpha-synuclein • nNeurodegeneration

Introduction

Parkinsonism is a clinical syndrome characterized by the occurrence of rigidity, postural instability, bradykinesia, and resting tremor. Although Parkinson's disease (PD), which is still the leading cause of parkinsonism, is characterized by these motor symptoms, other illnesses can also mimic them. Following Alzheimer's disease (AD), Parkinson's disease (PD) is the second most common neurodegenerative illness in the world. It is a crippling, progressive movement disorder characterized by degradation of the nigrostriatal dopaminergic system [1]. According to estimates, PD affects between 0.5% and 1% of people aged 65 to 69 and 3% of people 80 and beyond, with an annual incidence rate of about 11 cases to 19 cases per 100,000 people. The mechanism underlying motor manifestations is the progressive loss of dopaminergic neurons in the striatum and Substantia Nigra Pars Compacta (SNpc), with a minimum requirement of 60%–70% dopaminergic neuron loss. Patients may, however, show non-motor symptoms such as hyposmia, gastrointestinal issues, and sleep issues before the beginning of motor manifestations. The misfolding and aggregation of alpha-synuclein (-syn), the main protein component of Lewy bodies, is the neuropathological hallmark of Parkinson's disease (PD) (LB). The beginning of neurodegenerative processes is triggered by the creation of -syn protein clumps within brain cells. The interplay of aging, genetics, environmental factors, and infectious agents, such as viral infections, contributes to the multicomplex etiology of PD. Furthermore, a growing body of evidence exists to suggest viral parkinsonism, which frequently appears after recovering from viral illnesses. Viral parkinsonism and the pathophysiology of Parkinson's disease have both been linked to viruses, while the exact processes are yet unknown. Recent evidence suggests that one of these viruses may be the emerging human severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is to blame for the continuing epidemic that has already claimed the lives of more than 6.4 M people globally. The formation and subsequent spread of self-propagating pathological -syn aggregates throughout brain regions is the main feature of the "prion-like" cell-to-cell dissemination of amyloidogenic proteins, such as -syn, that has recently attracted significant attention in the quest to understand PD pathophysiology. This misfolded-syn spread mechanism has been supported by several in vitro experiments conducted on both continuous human cell lines and animal models. Since exosomes are already involved in several homeostatic processes in the Central Nervous System (CNS), such as myelination maintenance, synaptic plasticity, antigen presentation, signal transduction, neurogenesis, and trophic support for neurons, they have been proposed to function as an effective "vehicle" of transportation for such proteins. It's interesting to note that upon release from infected host cells, numerous viruses, including SARS-CoV-2, have been demonstrated to control exosomal biogenesis and cargo content. Additionally, research from our team and others suggests that virally modified exosomal cargo may serve as a template for disease development long after the viral agent has been completely eradicated, as a result of immune response-related or drug-mediated viral clearance [2]. We aim to highlight and discuss potential exosome-mediated mechanisms that may contribute to post-COVID-19 parkinsonism and PD pathogenesis in this review because exosomes play a significant role in the pathogenesis and diagnosis of neurodegenerative diseases and are known to be closely linked both to viral infection establishment and infectious disease progression even after virus eradication.

Viral infections as triggers for parkinsonism and PD development

Even though the underlying molecular and cellular mechanisms for PD and parkinsonism remain unknown, several studies have shown that viruses may play a role in their development. The emergence of encephalitis lethargica, an unidentified illness with a parkinsonian phenotype among survivors, and the Spanish flu were the first viral diseases to be linked to parkinsonism, according to historical records [3]. The development of Parkinson's disease (PD) or parkinsonism has been linked to several common human viruses, including the hepatitis C virus (HCV), herpes simplex virus type 1 (HSV-1), human immunodeficiency virus (HIV), varicella-zoster virus (VZV), West Nile virus (WNV), Japanese encephalitis virus (JEV), and Epstein-Barr virus (EBV). Notably, various in vivo and particularly in vitro studies have established the significance of the influenza A virus (IAV) in the genesis of the transient parkinsonian phenotype and the development of Parkinson's disease. An influenza diagnosis was associated with the emergence of Parkinson's disease (PD) 10 years later, according to a case-control study, and it was discovered postmortem in the substantia nigra of PD patients. Additionally, Parkinson's phenomenology, persistent microglial activation, and -syn aggregation caused by H5N1 infection in a rat model resulted in the death of dopaminergic neurons in SNpc. Similar to humans, mice infected with H1N1 showed persistent microglial activation as a marker of long-lasting virus-induced neuroinflammation that may eventually result in dementia. A subsequent in vitro work has shown that H1N1 replication can directly disturb protein homeostasis, causing -syn clumps in Lund human mesencephalic dopaminergic cells but failing to control TAR DNA-binding protein 43 (TDP-43) or tau protein. These findings strongly suggest that the H1N1 virus has a specific impact on -syn misfolding [4]. However, direct neuronal damage, persistent neuroinflammation, cerebral edema due to

virus-mediated damage to the brain endothelium, and induction of -syn aggregation have all been proposed as crucial neurobiological pathways of dopaminergic neuron loss and -syn pathology [3]. The key pathophysiological processes by which viruses contribute to the development of parkinsonism are still unknown. Notably, -syn has been proposed to be a natural antiviral defense mechanism for neurons because of its propensity to entrap viral particles and inhibit viral proliferation. In vivo tests with WNV-infected -syn-knockout mice demonstrated lower survival relative to the control group, lending support to this idea. Additionally, it has been proposed that viruses may use molecular mimicry methods to aggregate and form oligomers of -syn. When considered collectively, these findings provide compelling evidence that neurotoxicity and PD disease may be caused by virus-mediated neuronal deposition of pathogenic -syn. Since antibodies to these coronaviruses were discovered in the Cerebrospinal Fluid (CSF) of PD patients, the link between OC43 and 229E and other human Coronaviridae family members and PD has already been discussed [5]. The end of 2019 saw the emergence in China of the new coronavirus SARS-CoV-2, which led to an unusual viral pneumonia outbreak. This uncommon coronavirus disease, also known as COVID-19 or coronavirus disease 2019, spread quickly over the world due to its increased transmissibility and put a significant strain on public health. Even in the absence of COVID-19 symptoms, SARS-CoV-2 can spread through contaminated secretions like saliva and respiratory droplets when people come into direct, indirect, or close contact with infected patients. Although the majority of COVID-19 symptoms are systemic or respiratory, multiple investigations have shown that the condition can also cause anosmia, ageusia, altered consciousness, headaches, seizures, and paresthesias. According to several studies, COVID-19-related neurological sequelae may last for a very long time beyond the acute stage of infection. A syndrome known as "long" or "post"-COVID-19 syndrome develops beyond the acute infection period and is characterized by a combination of COVID-19-related symptoms that persist for more than 12 weeks. The Americans with Disabilities Act classifies these symptoms as a disability if another diagnosis cannot account for them (ADA). Numerous neurological symptoms, many of which are also present in Parkinson's disease (PD), such as weariness, brain fog, cognitive decline, and olfactory dysfunctions are included in the post-COVID-19 syndrome. Due to the neurological effects of COVID-19 and the immunopathological parallels between SARS-CoV-2 and other viruses connected to parkinsonism, such as influenza, it is fair to believe that these lingering symptoms could be a precursor to a post-COVID-19 new-onset neurological disease.

Parkinsonism and PD pathogenesis following COVID-19: potential roles for SARS-CoV-2-related exosomal cargo

Given the well-established involvement of exosomes in PD development and progression, post-COVID-19 parkinsonism, and likely PD onset via exosomal cargo, as well as its increasing significance in SARS-CoV-2 infection and propagation, we believe this area of research should be prioritized. The following two paragraphs outline and describe the potential functions of SARS-CoV-2-related exosomal cargos in the pathogenesis of viral parkinsonism and/or PD.

Induction of post-COVID-19 neuroinflammation and exosomal Cargo

After viral clearance and COVID-19 recovery, exosomes may be at the center of a neuroinflammatory turning point. Peripheral systemic inflammation and neuroinflammation are closely related, according to experimental research in several other systemic inflammatory diseases, including obesity and rheumatoid arthritis. Since exosomes may cross the BBB, they might serve as a physical link between these two disorders. Exosomes' ability to function as neuroinflammatory mediators in the presence of systemic inflammation has recently been demonstrated in vivo. In particular, brain gliosis, CNS expression of pro-inflammatory cytokine mRNA, and inflammation-associated miR-155 were all elevated in a mouse model that received serum-derived exosomes from animals challenged with Lipopolysaccharide (LPS). Additionally, it has been demonstrated that neurons and astrocytes can absorb exosomes produced by peripheral immune cells including active monocytes and macrophages, leading to the dissemination of pathogenic cargo and neurotoxicity [6]. In contrast to the control group, serum exosomes from people with Parkinson's Disease (PD) showed rising levels of IL-1 and TNF- inflammatory mediators. PD exosomes administered intravenously or intragastrically to mice caused -syn aggregation, microglia activation, and neurodegeneration of dopaminergic neurons, which exacerbated motor symptoms. However, glial cells can also leak exosomes that contain pro-inflammatory cytokines like IL-1. This sneaky exosomal cargo, which is derived from the glia, can spread to neurons and contribute to a vicious cycle of neuroinflammation and neurodegeneration, a condition that is further linked to getting older. Exosomes made from SARS-CoV-2-infected cells may contain inflammatory mediators that could enhance the model of neuroinflammation and subsequent neurodegeneration through peripheral systemic inflammation, possibly encouraging a cellular environment that favors the emergence and progression of PD mechanisms. Tenascin-C (TNC) and fibrinogen (FGB) levels in exosomes from COVID-19 patients were higher than in controls. When hepatocytes are exposed to exosomes from COVID-19 patients, TNC and FGB both cause the production of pro-inflammatory cytokines via NF-B signaling, resulting in the presence of TNF-, IL-6, and the chemokine CCL5. In this regard, it is important to look at any potential "window" of inflammatory insults to distant tissues. According to what is currently known, the SARS-CoV-2 S protein appears to play a crucial part in the regulation of neuroinflammatory events related to neurodegeneration by exosomes. As a result, plasma exosomes from COVID-19 patients were found to include S protein or S-derived fragments, with a higher exosomal presence in clinical cases with moderate rather than severe disease. Comparing infected individuals to the control group of healthy subjects, the multi-omics exosomal analysis found several molecules implicated in immunological responses, inflammation, and activation of both the coagulation and complement pathways [7]. Additionally, an in vitro experiment showed that ectopic expression of the SARS-CoV-2 S protein in HEK-293T cells led to the production of a significant amount of exosomes that were highly miR-148a and miR-590 enriched. These exosomal miRNAs reduced interferon regulatory factor 9 (IRF9) and ubiquitin-specific peptidase 33 (USP33) gene expression. USP33 is a Deubiquitinase enzyme (DUBs) and -a stabilizer of its target protein (IRF9). They internalized in human microglia cells and then deregulated the USP33-IRF9 network. Due to interferon (IFN)-mediated upregulation of IFN-like genes, IRF9 had previously been discovered as a protective functional protein in CNS homeostasis and its removal might cause severe neurological damage in glial cultured cells. The production of crucial inflammatory gene pathways like TNF-, NF-B, and IFN- was successfully generated by decreased microglial USP and IRF9 levels, which led to the activation of the neuroinflammatory cascade. In addition, exosomes isolated from the plasma of COVID-19 patients showed the presence of fragments derived from S proteins that are fully capable of eliciting an immunological response. Exosomes from patients with mild disease severity contained higher levels of MHC class II-antigen-presenting protein, which interacts with CD4+ T-cells to promote their proliferation and activation. IFN-mediated phagocytic conversion of brain myeloid cells can be brought on by MHC II upregulation, CD4 activation, and invasion of the CNS. A PD phenotype might result from the subsequent neuroinflammation and dopaminergic neuron loss in the SNpc. Exosomes that have been altered by SARS-CoV-2 may also contribute to neuroinflammation that is mediated by host regulatory mechanisms. Nuclear protein HMGB1 is involved in the control of autophagy, apoptosis, and numerous CNS processes like inflammation. HMGB1 concentrations in PD patients' serum and CSF are elevated. Notably, HMGB1 inhibition has been demonstrated to slow the development of PD pathology in PD animal models by reducing microglia-mediated neuroinflammation and neuron dopaminergic loss. Neurofilament Light Chain (NFL) levels are a biomarker for numerous neurodegenerative illnesses, including Parkinson's Disease (PD), and are a protein indication of axonal damage. NFL levels have also been linked to putative neuroinflammatory mechanisms that result in neurodegeneration in the early stages of multiple sclerosis development. High levels of HMGB1 and NFL were found in the exosomal cargo of neuron-derived EVs (NDEV) isolated from post-COVID-19 patients with or without neurological symptoms when compared to the control group, indicating that SARS-CoV-2 infection was responsible for controlling the two pro-PD development factors [8].

The development of parkinsonism and PD after COVID-19 Is promoted by the periphery-exosomes-CNS axis

Exosomes are fully capable of reaching difficult-to-reach neuroanatomical regions, including the olfactory bulb, the hypothalamus, the DMV, and the brainstem. They are loaded with SARS-CoV-2 components and RNA, as well as virally-induced neuroregulatory molecules. Retrograde axonal transport from peripheral neurons may

provide access to exosomes moving great distances from peripheral tissues that are important sites of infection, such as the lungs and intestine, to the brain. In that situation, SARS-CoV-2-related exosomes may end up interfering with normal homeostatic molecular mechanisms in brain regions previously linked to the pathogenesis of Parkinson's Disease (PD). A COVID-19 postmortem study found significant neurological damage but only trace amounts of SARS-CoV-2 RNA in the brains of patients who had already passed away. Additionally, in a SARS-CoV-2 intranasally infected hamster model, the cortical buildup of total -syn was seen after viral eradication without any signs of inflammation or neurotoxicity. According to the Braak hypothesis, any neurological sequelae and neuropathological outcomes seen in COVID-19 survivors could occur both directly from virus-induced effects and indirectly from molecular and neuroinflammatory mediators carried by exosomes linked to SARS-CoV-2 that continue to circulate even after the virus has been eradicated. According to Ahmed and colleagues, the neurological effects of SARS-CoV-2 infection may be related, at least in part, to the exosomal mRNA and Transcriptional Factors (Tfs) transported from the lungs to the brain regions [9]. This exosomal Tfs can modify the transcription of cellular genes and cause neural changes indicative of impending neurodegeneration. BCL3, JUND, MXD1, IRF2, IRF9, and STAT1 were discovered to activate genes linked to PD pathogenesis among the 19 exosomal Tfs found to be overexpressed during the acute phase of SARS-CoV-2 infection in key regions of the brain, including the medial and lateral substantia nigra and the superior frontal gyrus. These genes have been linked to several physiological processes, such as signal transduction, neuronal degeneration, and immunological monitoring. The pathophysiology of PD and neurodegeneration may be exacerbated by their Tf-mediated deregulation. For instance, STAT1 causes hypoxia-related microglia activation and dopaminergic neurons' autophagy, including hypoxia as shown by COVID-19. Exosomes may also play a role in the transport of protein expression regulators from the periphery, via the BBB, and into the CNS, which may explain the link between SARS-CoV-2 and PD. It has been proposed that these factors may interact with proteins associated with PD and are significantly expressed in the CNS. A pertinent investigation showed that SARS-CoV-2 virus proteins altered 24 host lung proteins to post-translational changes. Exosomes then engulfed and carried them from the lungs into the CNS, causing a local disruption of protein-protein interactions. The presence of SARS-CoV-2 viral proteins in brain-derived exosomes has also been confirmed by recent studies, potentially strengthening their function in SARS-CoV-2 transmission and pathogenicity. Compared to controls, all COVID-19-afflicted subgroups had considerably greater quantities of the crucial SARS-CoV-2 S1 and N proteins, according to cargo profiling of Neuron- and Astrocyte-Derived EVs (NDEV) retrieved from the plasma of patients. The group of patients who developed long COVID-19 with neuropsychiatric manifestations could be distinguished from the long COVID-19 group without these issues and the recovered COVID-19 patients without long COVID-19 using mean ADEV and NDEV levels of N protein. Furthermore, exosomes from recovered patients who had previously had both mild and severe COVID-19 were found to effectively display SARS-CoV-2 spike-derived fragments. DMV neurons are susceptible to oxidative stress in vitro studies, and oxidative stress increases intercellular -syn propagation. Through the use of SARS-CoV-2 S and N proteins, SARS-CoV-2 may use inflammatory exosomal cargo to cause oxidative stress in the DMV, increase -syn aggregation, and eventually advance post-COVID-19 parkinsonism. The two viral proteins have been demonstrated to enhance total -syn and Phosphorylation at Ser129 (pS129) levels, hasten the formation of amyloid fibrils by endogenous -syn, and ultimately produce LB-like disease [10]. These findings may lend support to this concept. It's feasible that the presence of these viral proteins in exosomes will reveal pathways that relate COVID-19 to PD when taken together. One could logically hypothesize that the COVID-19-related exosomal cargo could act as a neurodegenerative promoter and likely elicitor of parkinsonism manifestation given that SARS-CoV-2 viral components persist in exosomes during the acute and possibly the post-COVID-19 phase.

Conclusions

Numerous investigations have discovered a connection between viruses and parkinsonism, suggesting that they may act as an initial trigger of primary PD or secondary parkinsonism, even if the role of viruses in the pathogenesis of PD is still up for debate. The COVID-19 pandemic's emergence made it clear that, in many patients, the weight of post-COVID-19 symptoms does not always mean that the disease has ended when the virus has been eradicated after recovery. The possibility that SARS-CoV-2 infection could cause parkinsonism is one of the biggest worries for the medical community right now. This idea is strongly backed by the PD-like symptoms seen in some individuals during the acute or post-COVID-19 phase. We describe here clinical, inflammatory, and molecular overlaps that have begun to appear and form a neurobiological connective network between these two disorders, extending the idea of post-COVID-19-induced parkinsonian phenotype. Exosomes are important intercellular communication regulators and have been linked to neurodegenerative disorders. Exosomes are modified by SARS-CoV-2 so that they can act as a vector for viral dissemination by changing their cargo and, as a result, their function. Thus, these SARS-CoV-2-related exosomes may effectively convey SARS-CoV-2 genetic material and viral proteins into the CNS via BBB crossing from the periphery, such as the gut or lungs, or other tissues. Particularly SARS-CoV-2 related exosomes have the potential to transmit SARS-CoV-2 fragments, transcriptional factors, and inflammatory mediators to brain cells, leading to protracted neuroinflammation and -syn aggregation, which together contribute to the development of PD or a potential worsening in people with a genetic predisposition to the disease. Finally, we hypothesize in this review that cargo analysis of SARS-CoV-2-related exosomes, particularly related exosomes, particularly ones derived from the brain, could act as a compass for defining underlying virus-mediated pro-PD development mechanisms and for spotting the dreaded post-COVID-19 parkinsonism storm.

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