The Controversy Regarding the COVID19 Infection Causing Neurodegeneration, New Parkinson's Disease or Its Acceleration Remains Unresolved: a Narrative Review

Kulvinder Kochar Kaur[1*], Gautam Allahbadia[1], and Mandeep Singh[2]

[1]*Centre for Human Reproduction, India*

[2]*Department of Neurology, Swami Satyanand Hospital, India*

Received Date: May 20, 2022; Published Date: July 06, 2022

[*]**Corresponding author:** Kulvinder Kochar Kaur, Centre For Human Reproduction 721,G.T.B. Nagar, Jalandhar-144001, Punjab, India, E-mail: kulvinder.dr@gmail.com; Tel: 91-181-9501358180; Fax: 91-181-4613422

Citation: Kulvinder Kochar Kaur, Gautam Allahbadia1, and Mandeep Singh. The Controversy Regarding the COVID19 Infection Causing Neurodegeneration, New Parkinson's disease or Its Acceleration Remains Unresolved: a Narrative Review. ICARE. 2022;1(1):1005.

Abstract

The SARS-CoV2 pandemic has impacted the life of the population globally from 2020.The association amongst the new viral infection besides pathogenesis of various Neurodegenerative Diseases (NDD) got evaluated in different studies .In this review our objective was to carry out assessment, of the available publications regarding Parkinson's Disease (PD) and the COVID19 pandemic for provision of association amongst, the crossing of viral infection along with neurodegeneration regarding the present issue .Here we emphasize the SARS-CoV2 neurotropism, neuropathology, along with our belief regarding the association amongst infection, neurodegeneration in addition to the psychosocial influence of the pandemic in PD patients. Despite the corroboration of SARS-CoV2 pandemic in this review pointing towards a greater incidence of NDD In the future. Still existences of lot of controversies are there regarding enough outcomes for corroboration of COVID19 possessing the capacity of either result in stimulation of generation of new or exacerbation of the existent NDDs.

Keywords: SARS-CoV2; COVID19; Pandemic; NDD; Parkinson's disease; Viral infection;

Introduction

With the initiation of COVID19 certain doubts were raised regarding the Central Nervous System (CNS) involvement .Thus here we had the objective of provision of a summary in the context of association amongst COVID19, other viral infections as well as Parkinson's diseases subsequent to reviewing various aspects of Corona virus disease (COVID19) besides various neurodegenerative diseases [1-8] . Hence variable modes by which SARS-CoV2 viruses might impact various cerebral functions besides result in induction of neurodegeneration need to be taken into account.

I) The direct neurotoxic action of the virus that results secondary to neuro invasion is feasible in addition to actions due to systemic inflammatory changes. Initially we deal with the information with regards to SARS-CoV2 neurotropism, neuropathology, and neuro inflammation along with alterations in the amounts of biomarkers which have been found in the course of infection.

II) Subsequently we describe in brief the association amongst other viral infections along with Neurodegenerative Diseases (NDD), with our concentration being mainly on neurodegeneration, with attention centered on Parkinson's Disease (PD) in addition to cognitive impairment / Alzheimer's Disease (PD/ AD).

III) Finally we detail the impact of the pandemic on symptoms as well as psychosocial angle in case of patients with PD along with stress on the considerable influence of the infection in particular on individuals possessing prior neurological disorders in addition to disabilities.

Methods

Here we conducted a narrative review utilizing search engine PubMed, Google scholar; web of science; embase; Cochrane review library utilizing the MeSH terms like SARS-CoV2 ; COVID19; other viral infections ; Neurodegenerative Diseases (NDD); Parkinson's diseases; AD; from 1991 till 2021 till date from 1990 to 2022 till date.

Results

We found a total of 300 articles out of which we selected 124 articles for this review. No meta-analysis was done.

SARS-CoV2 Neurotropism

The etiological agent of the present pandemic is a member of the family Coronaviridae [1 rev by us].The earlier species of Coronaviridae (like HCoV-OC43), HCoV-229E, SARS-CoV, MERSCoV) were observed in human brain samples ,that corroborated their neurotropism along with them possessing the capacity of resulting in indelible infections of Central Nervous System (CNS) [9]. As early as 1999 it was illustrated that neuroblastoma, neuroglioma along with glial cells possessed proneness towards infection with human Coronaviridae in addition to the information that this virus possessed the capacity of lingering around for a minimum of 130 days of culture duration [9]. In case of animal models, this ineffaceable infection resulted in elimination of neurons in addition to long term consequences like reduction in action, besides volume of hippocampal neurons in the form of neurodegenerative phenotype [10-12].

A controversy is existent regarding SARS-CoV2 possessing the capacity of entering along with being indelible in cerebral structures. Actually certain results that corroborated the position of SARS-CoV2 neurotropism are detailed here. Regarding the Identification of Angiotensin Converting Enzyme (ACE2) receptor was the maximum common receptors observed for its entry [7]. Nevertheless, its expression is less prevalent in the brain in contrast to other tissues [13]. In CNS, its expression was illustrated on glial cells (astrocytes), capillary endothelium, monocyte/ macrophages, along with neurons[14].In contrast to this greater expression of ACE2) receptor was seen in the brain stem that resulted in the posit that invasion by SARS-CoV2 in brain stem structures might result in their impairment that are implicated in controlling CVS functions [15] . An infection of the ACE2 receptor in transgenic mice resulted in expression of viral antigen in neurons, in particular in thalamus, brain stem, and cerebrum; whereas cerebellum continues to be un afflicted [11].The influence brain regions illustrated neuronal depletion as well as microglial activation without any inflammatory signs [11].

Conversely escalated proof existed regarding ACE2 receptor might not be the primary viral invasion approach into the Central Nervous System (CNS). Rather other receptors might be implicated like neurolipin 1(NRP1) might aid considerably in SARS-CoV2 entry in cerebral structures [16-18]. Abundant NRP1 expression was observed in neurons along with astrocytes [17].

Three major routes had been suggested to result in SARS-CoV2 invasion in CNS are detailed hereafter [15,16,19].

The initial probable mode being, the transneural method initiated in the nasal epithelium along with olfactory nerve propagating into brain through axonal transportation [14]. This route of SARS-CoV2 neurotropism got illustrated for SARS-CoV2 along with HCov-OC-43 subsequent to intranasal infection [10,20].In transgenic mice expressing ACE2 receptor, SARS-CoV2 intranasal infection led to neuronal10,20] . Furthermore the mouse equivalent of the human Corona virus, the mouse hepatitis virus gained entry into brain through olfactory nerve following intranasal inoculation [21].

It was corroborated that neurotropism is the common mode that caused occurrence of olfactory impairment (OI) in COVID-19.Broad variable incidence of OI correlated with COVID-19(5-98%) was seen basically secondary to no objective evaluation [22]. Utilizing objective smell evaluation in 60 Iranian COVID-19 patients it got documented that 98% of them illustrated anosmia, however just 35% had subjective realization of their OI, emphasizing

the significance of objective evaluation regarding this symptomatology [23]. Gustatory impairment is frequent too in COVID-19 resulting in diagnostic dilemma with olfactory impairment [24]. Apparently OI is an early presentation during COVID-19 course [25]. Generally 2 modes might cause OI.

I) Blockade of the olfactory cleft via swelling or rhinnorrhoea that might not have been picked up in COVID-19 patients [23,24,26].

II) Defective sensorineural transmission might result in dysfunctional sense of smell [24]. With utilization of CT along with MRI imaging study in details in COVID-19 patients with protracted OI (least 1 mth) documented reduction in olfactory bulb volumes (43.5%) along with olfactory sulci being shallow (60.9%), thus corroborating this pathogenesis for OI in COVID-19 [26]. Nevertheless, there is lack of ACE2 receptor in olfactory sensory neurons along with their observation in supporting cells, sustenacular cells besides horizontal basal cells (alias reserve Stem Cells) in the olfactory along with respiratory epithelium [22]. This OI is usually a frequent symptom in elder patients occurrence of OI is in 10%of individuals >65 yrs along with in 62-80%in >80yrs [24]. OI is further realized to be a symptom of Alzheimer's Disease (AD) as well as Parkinson's disease (PD) [24]. Intriguingly OI in COVID-19 takes place more frequently in younger patients possessing inverse association with demise [27]. This corroborates with the posit that is in contrast regarding OI being a sign of defense against the virus for avoidance of the arrival of the virus in the cerebral structures instead of just avoidance of entry in the CNS [28].

B)

I) The other alternate transneural method of invasion approach in CNS by SARS-CoV2 implicates the trigeminal or vagal nerve has further got described.

II) The second route suggested for CNS viral invasion is the hamatogenous route that gets followed by crossing of the Blood Brain Barrier (BBB)/choroid plexus infections [15,16,19]. This has been detailed regarding other viruses like HIV, HSV, and HCMV besides enteroviruses [12]. In this particular route endothelial cells in blood vessels besides choroid plexus might be the invasion target in view of expression of ACE2 receptor demonstrated in them [16]. Furthermore the spike protein of SARS-CoV2 might cross along with result in impairment of the BBB by stimulation of an inflammatory response amongst the micro vascular endothelium [29]. The other mode validating this route might be enhanced permeability of BBB secondary to escalation of interleukin-6 (IL-6) amounts, existent in acute COVID-19 disease [19,30].

III) The third probability regarding pathway of SARS-CoV2 neurotropism is what is referred to as the ''Trojan horse mode''-detailing the viral infection of immune cells (neutrophil, monocyte, macrophages,CD4+ lymphocytes) that arrive in the CNS via blood stream followed by migration into cerebral structure by diapedesis [15-17].On arrival in the cerebral tissue, the virus/viral particles might get liberated by these immune cells [16].

Neuropathology of SARS-CoV2

Usually Neuropathological cornerstone of COVID-19 autopsy patients reveal generalized oedema, gliosis with microglial along with astrocytes activation, ischemic damage, intracranial bleeding, arteriosclerosis, hypoxic ischemic damage, encephalitis /meningitis along with diffuse inflammation [31]. COVID-19 patients presenting with robust disease illustrated decreased neuronal amounts besides escalated activated microglial along with astrocytes amounts in addition to greater pro inflammatory cytokines as estimated byqPCR [32].

In parallel with posit of hamatogenous route of invasion brain, Paniz Mondolfi et al. [33] Isolated this virus in capillary endothelium along with neurons from frontal lobe tissue in COVID-19 patients [16,33]. *In vivo* virus was not observed in glial cells [16]. Akin observation was of SARS-CoV2 preference in CNS endothelial cells by identification of ACE2 receptor expression in smooth muscle of blood vessel [34]. In5/9 patient's small blood vessel disease was seen in autopsy patients; Nevertheless, SARS-CoV2 was found in a lone case with utilization of Immunohistochemistry [35]. Utilization of PCR in brain for estimation of SARS-CoV2 was tough as well; maximum viral load was seen in the olfactory bulb, whereas SARS-

CoV2 PCR was negative continuously in the substania nigra [28,34,36]. Nevertheless, observation of viral existence was occasional in viral encephalitis usually (like herpes virus, arbo virus, entero virus stimulated encephalitis) [12].

COVID-19 brains on autopsy patients revealed microglial activation in olfactory bulb, frontal, hippocampus with maximum load seen in the brain stem, while no activation of lymphocytes was visualized apparently [35]. Intriguingly, patients with history of delirium at the time of COVID-19 illustrated greater microglial activation in the hippocampus [35]. Those patients whose presentation were with/ without sepsis were not feasible neuropathologically that countered the usual posit of neuropathology generation secondary to a cytokinestorm at the time of septic disease [35].

SARS-CoV2 Neuroinflammation along with Biomarker

Besides direct impact of SARS-CoV2 on brain by CNS invasion, the remaining actions on cerebral functions secondary to systemic change in the disease course have been broadly described. Brain tissue along with biofluids investigations besides the systemic response demonstrated a neuro (inflammatory) reaction initiated by COVID-19. Escalation of numerous cytokines in the blood at the time of acute COVID-19 were seen, whereas enhanced pro inflammatory markers amounts were not found in the cerebrospinal fluid (CSF) [37]. Serum amounts of IL-4, IL-10, IL-6, along with IL-1β were escalated in patients of COVID-19 [29,38]. Knowledge is existent regarding IL-1β as well as IL-6, possessing the capacity of stimulating Neuroinflammation [14].

Common determination of SARS-CoV2 COVID-19 patients was observed despite its incapacity of corroborating g intrathecal antibody generation [37,39,40], Determination of virus by the quantitative polymerase chain reaction(qPCR) from CSF was not feasible in maximum patients [41-44,5], Description of sporadic positive outcomes obtained in SARS-CoV2 PCR from CSF was documented rarely by authors in patients with robust cerebral symptoms [41].

Evaluation of markers pointing to CNS injuries documented escalated amounts of Neurofilament Light chain (NfL) along with Glial Fibrillary Acidic Protein (GFAP) in plasma of patients with moderate to robust COVID-19 [17,45]. Moreover 3/8 patients with robust COVID-19 displayed signs of break down in blood brain barrier, one possessed particular intrathecal antibody generation ,while 4 illustrated positivity for 14-3-3 in the CSF [44].The outcomes of CNS pleocytosis were contradictory thus far. In a case series comprising of 15 patients besides a review described CSF WBC counts in 409 COVID-19 patients presenting with neurological symptoms found commonly pleocytosis (by definition>5 cells /μL) in 36% of 15 along with 17% of 409 patients [30,46]. Conversely a case series comprising of 13 patients with COVID-19 as well as encephalopathies / convulsions documented CSF pleocytosis in a single patient only akin to a study comprising of 18 patients of COVID-19 along with neurological complications observed pleocytosis in 4patients besides documenting that all 4 were most probably secondary to blood contamination [47,2].

Assessment of cargo of neuronal-enrichment of Extra Cellular Vesicles (ECV's) was conducted by Sun et al. Intriguingly they found enhanced NfL, amyloid-β, neurogranin, tau as well as phosphorylated tau in COVID-19 patients pointing to a neurodegenerative event [42].

Viral Infections along with Neurodegeneration

Other than the COVID-19 pandemic, a wide epidemiological corroboration associating other viral infections with Neurodegenerative Diseases (NDD), particularly of PD as well as AD exists.

The thought that viral infections possess the capacity of facilitating neurodegeneration was initially generated with encephalitis lethargica subsequent, to Spanish flu epidemic at the initiation of 20th century. Following that an association amongst infections with NDD got assumed repetitively.

A meta-analysis of 287,773 patients with PD along with 7,102,901 controls documented that the patients with documented infections earlier possessed escalated risk for PD (odds ratio, 1:20) [44]. Bacterial infections were believed to be implicated for these actions [44]. In agreement another recent study observed a "greater infectious burden", that by definition was the presence of greater antibodies against various viruses along with bacteria in blood of PD patients [48] .With in particular PD

risk was demonstrated to be escalated subsequent to VZV infections (adjusted Hazard Ratio [HR], 1:17) as well as PD patients possessed seropositivity with greater probability for EBV [49]. HCV has been a well documented factor for PD , like HSV1infection for AD generation [50,51].

Influenza viruses were further correlated with PD, as encephalitis lethargica possessed a Parkinsonian phenotype along with Influenza virus was posited to be the etiological agent regarding Spanish flu [52,53]. Moreover H1N1 infection resulted in continuous microglial activation in the form of chronic Neuroinflammation in case of wild kinds of mice [45]. H1N1 thus caused microglial activation along with α-synuclein accrual in mice leading to dopaminergic neuronal depletion in the substania nigra, which is believed to be the pathological landmark of PD [46]. Additionally, Influenza virus was observed in the autopsy of PD patients in substania Nigra [47]. Utilization of outcomes of a recent case control study from the results of a Danish National patient registry illustrated that there was a correlation amongst diagnosis of Influenza with the generation of PD upto 10yrs subsequently (OR1.73) [52] .Thus this robust correlation existence however requires greater evaluation.

Japanese encephalitis virus results in Parkinsonian phenotype at the time of acute disease, however continued Parkinsonism with MRI wounds in the substania nigra was seen 3 years to 5 years subsequent to the Viral Infection [53].

Induction of Parkinsonism by West Nile virus is feasible at the time of acute infection. In post mortem evaluation escalated α-synuclein amounts were seen in patients infected with West Nile virus [49,54]. An Intriguing posit regarding α-synuclein function was generated in an α-synuclein knockout mouse model subsequent to the West Nile infection [54].The lack of α-synuclein in this model resulted in dramatic propagation of the disease pointing to α-synuclein confers protection against Viral Infection [49,54]. The posit given was entrapment of viral particle by α-synuclein in the form of a cellular defense mode, that continues subsequent to the infection resulting in its pathological accrual followed by neurotoxic actions. The akin mode was posited for β-amyloid that possesses the capacity of entrapment of HSV1 besides hampering its viral replication along with entry *in vivo* as well as *in vitro* [55]. Disease risk factor was attributed to HSV1 infection greater in AD however in PD as well in variable *in vivo* as well as *in vitro* evaluation [56]. Enhancement by 2.56 times risk factor for dementia generation was documented in a retrospective cohort study, comprising of 8362 patients with acute HSV1 or HSV2 infection [51]. A phase 2 study evaluating if vaciclovir possesses the capacity of reduction of propagation of AD in patients with HSV1 is presently continuing (Clinical trials. gov NCT03282916) [55].

Various studies are existent pointing to implication of adaptive immune system in the generation of neurodegeneration. Genome Wide Association Studies (GWAS) observed correlation of particular major histocompatibility complex II gene alleles with PD as well as T cells of patients with PD were illustrated to react with α-synuclein epitope [57]. Demonstration of Th17 T cells aiding in PD pathogenesis in a cell culture with utilization of induced pluripotent Stem Cells (iPSCs) was done by another group [58]. Recently T-cells were observed to be neighboring the Lewy bodies in addition to dopaminergic neurons in brains of Lewy bodies dementia patients along with stimulating CD4+ T cells with a phosphorylated α-synuclein epitope caused escalation of IL17 generation as a sign of Th17reaction [59].

Usual Impact of SARS-CoV2 in Neurodegeneration

The earlier described mode of viral neurotropism along with Neuroinflammation stimulate a query regarding long term neurodegeneration has to be anticipated subsequent to COVID-19 disease.

SARS-CoV2 along with pathogenic proteins possessing the potential of impacting neurodegeneration has been correlated in various studies. It was found that spike protein receptor binding domain binds to heparin as well as heparin binding proteins inclusive of, -amyloid β, α-synuclein, tau, prion besides TDP-43 which might precipitate the pathological accrual of these proteins leading to neurodegeneration [60]. Akin mode has been detailed regarding HSV1 that catalyzes the accrual of amyloid β *in vivo*, as well as *in vitro*, having been well documented risk

factor for AD [60]. Recent illustration was that viral particles (inclusive of SARS-CoV2 spike protein) promoted the transmission of proteopathic seeds by changing intercellular cargo transport [61].

Variable approaches utilized for snatching the regulation of host cellular functions like disrupting autophagy besides mitochondrial or lysosomal function that are responsible for generation of NDD also [62]. SARS-CoV2 changes autophagy besides mitochondrial or lysosomal function in lungs that are infected [63].

Moreover viral alterations of proteastasis in the host cell can result in escalated aging of the infected tissue that might further accelerate the neurodegenerative event, often visualized in senescent cells [62].

Ferro senescence represents an iron modulated premature aging event of cells causing iron stimulated disturbance of DNA healing that gets followed by neurodegeneration [64]. This represents an intriguing capacity of virus of inducing ferrosenescence in host cells causing facilitation of viral replication [64].

COVID19 along with Potential Modes Associated with Parkinson's Disease

There are various correlations amongst COVID19 along with the generation of PD described further.

That the mouse hepatitis virus (isolated as a murine analogue of human Coronaviridae) was found to result in mild encephalitis besides viral antigen got deposited mainly in the nucleus subthalamicus as well as substania Nigra [65]. Following gliosis in these areas was pointing to a correlation amongst the virus along with PD or post encephalitic Parkinsonism [65]. Escalation of antibodies against Coronaviridae was observed in the CSF of patients with PD in contrast to controls by 1992 itself [66].

The documentation of 3 case reports of PD initiation at well timed association with COVID19 disease. Nevertheless, no clear cut etiological association could be found [67].

2 patients generating COVID19 correlated encephalitis with propagating atypical Parkinsonism as well as FDG-PET changes reminding of post encephalitic Parkinsonism got published [68].

Numerous modes by which COVID19 might aid in the generation of PD got reviewed ;i) Vascular injuries in the nigro striatum might occur following Parkinsonism [69]. Moreover the cytokine storm correlated with robust COVID19induced neuro inflammation, followed by neurodegeneration [30,69]. Systemic amount of IL-6 were enhanced with a small prospective observational study showed a greater amount of IL-6 is correlated with an escalation of generating PD [70].

The other plausible mode of PD induction might be viral neurotropism leading to direct neuronal injury in important regions. IPSC obtained mid brain dopaminergic neurons were illustrated to be prone to SARS-CoV2 infection, that initiated an inflammatory response followed by cellular senescence *in vitro* [71]. RNA sequencing evaluation of the ventral mid brain tissue of COVID19 patients illustrated an akin phenotype of neurons which were inflamed besides Identification of low amounts of SARS-CoV2 transcripts [72]. These outcomes emphasized regarding particular proneness to SARS-CoV2 of specifically susceptible mid brain areas implicated in the generation of PD.

The usual proneness of CNS structures to SARS-CoV2 was illustrated by Ramani et al. [72] Where brain organoids were infected besides observation of viral entering in particular in neurons .The infections followed by neuronal demise [73].

An association amongst nuclear factor κB (NFκB) along with PD have been illustrated earlier since NFκB was enhanced in the substania nigra of mice who received MPTP treatment [74]. MPTP treatment is usually employed in an animal model of PD since the neurotoxin resulted in nigro striatal degeneration in addition to depletion of dopaminergic neurons [74]. In this model NFκB suppression caused avoidance of dopaminergic neuronal degeneration [74]. Treatment of dopaminergic neurons in an *in vitro* model with 6-OHDA caused activation of NFκB along with caspase besides apoptotic demise that got avoided by hampering NFκB [75]. SARS-CoV2 activates NFκB through pattern recognition receptors that might initiate neurodegeneration [75].

Other intriguing issue is the common involvement of dopamine- angiotensin aldosterone system in COVID19

along with PD. generation of Angiotensinogen occurs in astrocytes in the form of local Renin-Angiotensin Aldosterone System (RAAS) [76]. Pathological over activation of this (which further occurs secondary to dopaminergic neurons degeneration) resulting in Oxidative Stress (OS) as well as inflammation while hampering it was believed to be an approach regarding treatment in various neurodegenerative diseases inclusive of PD as well as AD [77], In view of utilization of ACE2 receptor for entering host cells, it causes disturbance in RAAS also [15].

A prior found association amongst H1N1 Influenza virus along with α-synuclein accrual might probably possess importance for SARS-CoV2 as well. H1N1 resulted in accrual of endogenous α-synuclein in LUHMES cells [78]. The explanation for the pathological α-synuclein accrual subsequent to H1N1 infection dysfunction of autophagosomes of infected LUHMES cells was posited [79]. Intriguingly α-synuclein accrual was visualized in the olfactory bulb subsequent to intranasal delivery of H1N1 [79].

Early symptomatology of PD is olfactory along with vegetative impairment inclusive of obstipation in addition to prodrome syndrome REM sleep Behaviour Disorders (RBD). Olfactory impairment is a frequent early symptom of COVID19 along with olfactory route is described as a way of entering CNS [21,25]. Hence apparently it is a probability regarding COVID19 impacting the pathogenesis of PD since SARS-CoV2 might use a route for spread as described in generating neuropathogenesis of PD [80].

Polysomnographic evaluation in 11 patients subsequent to 4 months of originating infection with SARS-CoV2 documented REM sleep events without atonia in 4 patients that is a typical (prodromal) sign of RBD.

Other intriguing issue is the association of gut microbiota(GM) along with its dysbiosis in the generation of PD [81]. SARS-CoV2 results in dysbiosis as well as intestinal inflammation pointed by escalated fecal calprotectin in COVID19 correlated diarrhea that posits a probable association with PD [82]. In around 50% of patients with COVID19 SARS-CoV2 RNA was observed in the faeces, corroborating the position of intestinal infection [83].

Molecular evaluations have corroborated association amongst COVID19 along with PD concentrating on protein crosstalk. In toto 44 proteins in CNS responsible for PD were observed to crosstalk with 24 host proteins from the lung which crosstalk with SARS-CoV2 viral proteins [84]. The 2 maximum attractive crosstalk candidate proteins were Rab7a along with NUP62 [85]. Rab7a represents a lysosomal protein which decreased the percentage of cells with α-synuclein particles along with α-synuclein toxicity while NUP62 is implicated in autophagosomes generation [85]. The contrasting of transcriptomic manipulation induction by SARS-CoV2 along with PD further displayed important overlap in various pathways [86].

Conversely part of α-synuclein in conferring protection from COVID19 was posited as α-synuclein like amyloid β are up regulated on the arrival of virus infections besides limiting viral replication in the form of a defense mode in the brain [87]. Prior to the COVID19 pandemic, a Japanese retrospective cohort study illustrated that patients of PD that were hospitalized possessed lesser probability of demise from pneumonia in contrast to others [88].

In case of α-synuclein up regulation in viral infections in the form of a defense mode it might be resulting in continued inflammation along with neuronal demise that triggers the generation of PD in long time, the way illustrated for West Nile virus infections [69].

Intriguingly, a posit regarding association amongst COVID19 along with atypical Parkinsonism might be drawn despite restricted results thus far. It got illustrated regarding atypical Parkinsonism like atrophy of numerous systems as well as propagating supranuclear palsy are correlated with microglial activation in the form of signs of Neuroinflammation besides microglial activation aiding in neurodegeneration [89]. That microglial activation can get observed with utilization of PET imaging which might work like a biomarker for tauropathies [90]. Microglial activation along with Neuroinflammation is observed in COVID19 (already detailed) that makes an association amongst Parkinsonism along with COVID19 [35].

Alzheimer's disease, Cognitive Deficiencies along with COVID19

Proof that have been accumulated illustrated an intricate association amongst cognitive interference along with COVID19 .A prospective longitudinal, study documented that cognitive reduction as determined by Montreal Cognitive Assessment (MOCA)was found in 21% of mild COVID19 patients *vis* a *vis* 2% of seronegative persons [91]. In a different study pathological MOCA outcomes were observed in 18/26 COVID19 patients along with FDG-PET-aberrations (front parietal hypo metabolism) in 10 patients which matched the clinical deficiencies [40].

Besides observation of cognitive reduction at the time of acute infection documentation were further revealing of continued cognitive dysfunction subsequent to recovering from COVID19 since MOCA aberrations were found in a group of patients in the post COVID19 duration for a minimum of1mth subsequent to release from hospital [71]. Akin to that 46/57 COVID19 patients undergoing recovery (81%) revealed signs of cognitive dysfunction [18,92]. Intriguingly continued memory along with concentration abnormalities was further observed subsequent to SARS-CoV1 as well as MERS infection in 15% to 20% patients [93].

Utilization of transcranial magnetic stimulation for assessment of patients recovering from COVID19who had developed robust COVID19 infection needing ICU admission in addition to neurological complications documented fatigue besides illustrated aberrant scores in the frontal evaluation battery at the time of subacutephase [94]. This transcranial magnetic stimulation documented dysfunctional GABAergic intracortical circuits whereas glutamatergic transmission was alright [94]. GABAergic dysfunctions are generally frequent in front temporal dementia along with executive impairment [94]. Nevertheless noticeably cognitive dysfunction is frequent subsequent to Acute Respiratory Distress Syndrome (ARDS) that might possess numerous explanations rather than COVID19 [71,95]. Subsequent to ARDS cognitive impairment continued in long time follow up in around 10% of patients [71]. In other different studies cognitive deficiencies along with psychiatric abnormalities (basically depression as well as anxiety) I were found in uptill 60% of patients who survived following ARDS subsequent to 12 months [96].

Dementia was observed to be the maximum robust risk factor for COVID19 along with correlated with greater mortality [97,98]. As such dementia patients face problems regarding hygiene sustenance, mask needs, behavioral directive along with rules regarding maintaining distance in view of cognitive deficiencies [95]. Usually dementia patients are placed in nursing homes with a greater risk factor for acquisition of infection in numerous areas [95]. COVID19 disease in patients with dementia usually seemed to have atypical presentation mainly with delirium/confusion along with occasional symptom regarding infection [98]. Confusion along with mood as well as behavioral impairment continued in 19.2% survivors [98].

An assessment of the networks dependent association regarding gene / protein setups amongst virus as well as host factors along with various neurological diseases in an interactome model illustrated intricate association amongst COVID19 along with cognitive reduction besides PD as well as AD [18].

Post mortem studies illustrated that expression of ACE2 was escalated in brains of patients with AD. In particular in robust dementia expression of ACE2 was escalated that might result in greater proneness to COVID19 [95].

Injury of White Matter (WM) that is ischemic, taking place early in AD aids in the propagation of dementia. Induction of vascular damages is feasible with COVID19 in view of hypercoagulability besides can be anticipated to cause exaggeration of disease propagation in patients of AD [99].

It got posited that amyloid β, the protein responsible for AD generation represents an antimicrobial peptide implicated in avoidance, of cerebral SARS-CoV2 infection as detailed regarding α-synuclein, for PD [78]. It might be pointed that there is upregulation of amyloid β in the form of a defense mode at the time of infection resulting in over activation of besides pathological amyloid β getting deposited in the longer time duration [78].

Additionally, Apoε4 is a corroborated risk factor for AD was further believed to be a significant risk factor for COVID19 probably associating the 2 pathophysiological conditions [100]. Greater proneness to SARS-CoV2 infection in human induced pluripotent Stem Cells (iPSCs) models possessing Apoε4, genotypes neurons along with astrocytes had greater pronenessto SARS-CoV2 infection in contrast to non Apoε4cells beside brain organoids [17].

An alternate overlapping mode is IL-6 which was illustrated to be escalated in COVID19 along with believed to be a biomarker possessing prognostic importance in AD [49,101].

Probably SARS-CoV2 causes interference with autonomic functions in vagal control centers in the brain stem [97]. Autonomic functions are dysfunctional in AD as greater cardiac sympathetic functions along with lesser parasympathetic functions have been documented in patients [97]. Thus non auricular vagal stimulation has been detailed in the form of therapeutic approach for AD, besides robust COVID19 ,as a down regulation of inflammatory pathways(decreased IL-6 amounts)is anticipated secondary to that [97]. Corroboration of this posits transauricular vagal stimulation possessed the capacity of decreasing cognitive impairment in a pre clinical murine model of AD [102].

AD causes changes in calcium homeostasis in the brain; akin mode is utilized by RNA viruses for promoting viral replication .Thus viral replication might be simpler in AD patients, possessing aberrant calcium homeostasis beforehand [103]. A correlation is amongst Diabetes type II along with AD that escalates the risk for AD generation [103].

Parkinson's disease along with COVID19: Actions of COVID19 Symptoms: Psychological Besides Social Issues

The action of the pandemic regarding day to day life was significant worldwide besides patients with chronic diseases(required continued care were in particular influenced .A detailed assessment of global studies (with n=210,419 enrolled patients) illustrated that the acute care regarding neurological situations were interfered with secondary to the pandemic in 47.1% of subjects. Differential influence on PD patients was detailed since particular issues took place as a link amongst pandemic correlated limitations. Psychological problems besides issues correlated with care along with medicines dissemination were observed to be maximum taxing regarding this cohort [104].

COVID19 possesses the capacity of changing the pharmacodynamics of levodopa further secondary to diarrhea, a usual symptom of COVID19. This resulted in motor variations in PD patients which were infected [105]. PD patients afflicted with COVID-19 frequently generated a post COVID syndrome (85.2%) presenting with deteriorated motor functions along with escalated levodopa dosage needs, fatigue, reduction in concentration in addition to interference with sleep [106].

Nevertheless subjective deterioration of motor besides non motor symptoms of PD patients were not influenced by COVID19 at the time of the pandemic was further documented in various studies [84,107]. Furthermore, new behavioral symptoms were seen in 26% of PD patients in an Italian cross-sectional study [107]. Loneliness feeling as well as feeling of deprivation beside lack of interactions with the treating doctor was felt [84].

It was posited that dopamine based adapting is needed regarding tackling situation successfully hence PD patients possess lesser flexibility besides encountering greater problems for adapting to the new milieu [6]. Hence the pandemic might result in stress in PD patients having to cope with adaptation to a new milieu rapidly. Psychological stress was illustrated to cause deterioration of PD symptoms besides the effectiveness of dopaminergic medicines in particular regarding the tremor [108]. This might be the reason for the exaggeration of symptoms in the PD patients at the time of the pandemic.

It was the observation that 103 patients of PD documented 4 major difficulties at the time of the initial lockdown i) scared of acquisition of COVID19 ii) decreased physical activity iii) incapacity of acquisition of support services besides the clinics iv) decreased socialization [109]. An objective decrease in physical activity as determined with the

utilization of a smart phone application in view of maximum PD patients were not able to perform 30' of daily activity [110]. More exacerbation was seen in 44% at the time of being confined .That physical activity as well as training is a significant treatment approach for sustenance of motor symptoms as well as independence, thus physical activity avoidance at the time of lockdown can be anticipated to cause symptoms propagation besides deletion of independence [110].

Furthermore, in 66% of PD patients from a large cohort from the Colombia University documented mood along with sleep interference during pandemic, depression as well as insomnia was the commonest documented in numerous other studies also [111,112]. A Chinese study displayed that PD patients presentation was greater sleep interferences along with anxiety in contrast to healthy controls besides these symptoms having independent correlation with acceleration of other PD symptoms [112]. Sleep issues were further correlated with a bad Quality of Life (QOL) [111].

Interventions dependent on mindfulness were illustrated to result in reduction of depression along with anxiety, besides enhancement of motor symptoms [108]. In view of achieving this feasible with virtual means apparently it might work out as an attractive therapeutic approach currently besides in future [108].

The numbers of hours correlated with care provision enhanced markedly at the time of the pandemic. Family members were the major providers of care [113]. In the COVID19 period pressure of care provision enhanced considerably [107]. Intriguingly, Montanaro et al. as well as others illustrated that depression along with anxiety were common in PD patients besides their providers of care [114]. In 35% of PD patients depression existed besides in 21.7%of care providers, while 37% of PD patients along with40% of care providers presented with anxiety [114]. Thus greater support was the requirement for care providers in particular at the time of the pandemic for tackling their own enhanced tensions besides the neuropsychiatric issues of their relatives [115].

Nevertheless COVID-19 by itself had no influence on PD symptoms it was further described regarding prior existent PD possesses the capacity of escalating the risk of mortality/case fatality onSARS-CoV2 infection despite contradictory result regarding this issue [116]. The time period of ICU stay/hospitalization besides ventilation further were not variable in PD patients besides non PD COVID-19 PD patients in a large assessment of COVID-19 German inpatients [117]. The Italian study contrasted COVID-19 patients with PD to COVID-19 patients without PD, observing no variation in mortality (5.7% for PD COVID-19 patients expiring *vs* 7.6% non PD COVID-19 patients) [118].

This tendency might be corroborated by the posit regarding amantadine besides entacapone might confer protection against COVID-19 that was pointed by various studies [119]. Nevertheless a systematic review regarding 1061 greater in COVID-19 patients corroborated greater hospitalization rate, case fatality as well as mortality rates for these in contrast to non PD COVID-19 patients [120]. The short come of this study was no matched age that is anticipated to impact the outcomes in view of age being a confirmed risk factor case fatality as well as mortality rates for regarding COVID-19 [120]. An American study contrasted 78,355 non PD COVID-19 patients with 694 COVID-19 patients with PD, observed escalated mortality despite adjustment as well as match for age along with sex [121]. A muticentric German study illustrated that both prevalence as well as mortality of COVID-19 patients was greater in PD in contrast to non PD COVID-19 patients [122].

These results seem to not yield if these PD COVID-19 patients are at a greater risk for robust COVID-19 infection cannot be decided at this juncture. Noticeably PD patients suffering from COVID-19 have greater chances of presentation with atypical symptom like mood alterations, fatigue, joint ache as well as acceleration of PD symptoms that might add complexity regarding the diagnosis of SARS-CoV2 infection [123].

Newer onset Parkinson's disease in COVID-19

Parkinsonism symptoms secondary to the generation of COVID-19 are occasional with proof associating COVID-19 to generating PD presently is simply a posit. Goerttler et al.

[124], scanned the literature regarding the description of newer onset PD that correlated with COVID-19, observing 6 patients with new Parkinsonism motor symptoms, of which 5 presented with corroborated dysfunctional dopaminergic uptake in the basal ganglia subsequent to nuclear imaging (Figure 1).

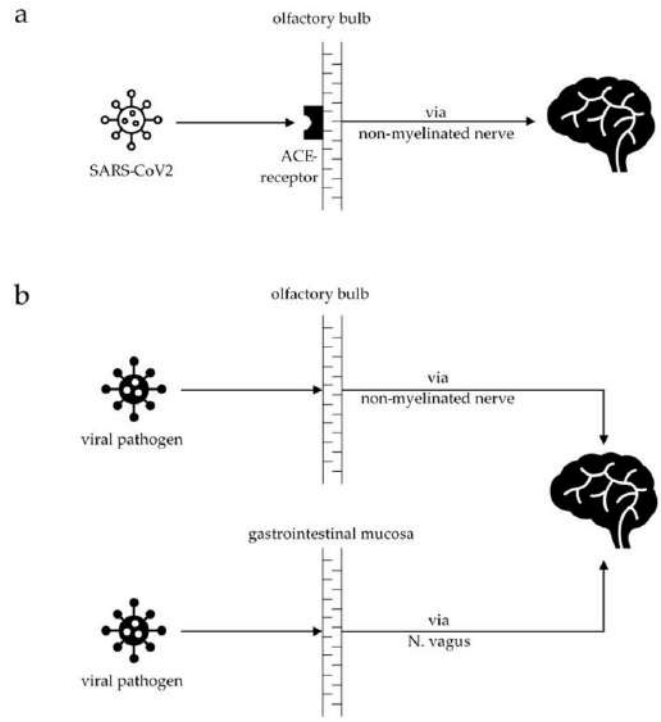

Figure 1: Courtesy ref no- 124-Schematic diagram of the potentially harmful pathway in COVID-19 and Parkinson's disease (PD):

a. The SARS-CoV-2 virus enters the brain via the olfactory bulb, binding to the ACE receptors. From there, it spreads via non-myelinated nerves into the brain.
b. In PD, there are two hypothetical, not yet fully understood, routes that the viral pathogen can use to enter the brain, either via the olfactory bulb ("brain-first" theory) or via the gastrointestinal mucosa ("body-first" theory), spreading into the brain via the vagal nerve.

Nuclear imaging(with the utilization of FP-CIT-SPECT besides F-DOPA-PET in 5 of the patients displayed proof regarding the implication of basal ganglia with chronic dysfunction of dopaminergic transmission secondary to nigro striatal degeneration that was responsible for motor symptoms[rev in 124]. In a patient FDG- PET imaging documented diffuse hypo metabolism with considerable hypo metabolism in the precuneus, that had maximum probability of being correlated with Alzheimer's disease [124]. Correspondingly, this subject illustrated Cognitive reduction at the time of propagation of COVID-19, however, further illustrated comparative hyper metabolism in the basal ganglia, like commonly seen in PD patients [124]. Acute encephalitis patients further displayed hypermetabolism in the impacted brain regions followed by hypometabolism subsequent to recovery [124]. Hence in this patient hypermetabolism in the basal ganglia had maximum probability of being an encephalopathic event. 2 patients responded well to dopaminergic medicines pointing to the dysfunction possessing the capacity of responding to substitutingdopamine,that corresponded to nuclear imaging observations.

Absence of follow up for outcomes in these patients did not corroborate the existence of a propagating Neurodegenerative disease. Nevertheless, a minimum of 1 patient achieved full remission of the PD symptoms [124], pointing to the feasibility of the existence of an acute reversible disorder. Conversely nuclear imaging illustrated dysfunctional dopaminergic transmission in all the patients studied. Moreover in a patient antecedent symptoms (like constipation) existed [124], pointing to the existence of prior PD not having been diagnosed has to be taken account despite constipation might not be a particular antecedent symptoms, which might be secondary to other etiologies.

Conclusions

Thus the restriction was maximum studies were conducted with outcomes regarding PD patients along with COVID-19 were collected just for the initial 6 months of the pandemic with uptill 2500 patients cohort &none to minimum follow up further inext few months/yrs. Simultaneously millions of COVID-19, patients documented globally with anticipation of similar enhancement of PD patients to rise. This gap requires filling for drawing any meaningful association amongst PD & COVID-19.

Regarding the 2nd restriction was that maximum evaluated studies on PD along with SARS-CoV2 usually had

investigated patients with idiopathic Parkinson's disease however no proof regarding the atypical Parkinson's disease were observed.

As per Goerttler et al. [124], data Parkinson's symptoms do not usually take place in patients with post COVID-19 syndrome. The detailed lurking post pandemic, as took place over a century back can't be corroborated at present stage however needs evaluation in the future.

References

1. Kulvinder Kochar Kaur,Allahbadia GN,Singh M. "Iridoids. Some Monotepenes and Other Natural Products for Development of Potential Therapiesin Alzheimer's Disease-A Review". Nutrition and Food Toxicology. 2019;3(5):741-56
2. Kulvinder KK, Gautam A, Mandeep Singh .A comprehensive review on epidemiology, aetiopathogenesis, diagnosis and treatment of the novel coronavirus syndrome – COVID-19 Iberoamerican Journal Of Medicine. (2020)
3. Kulvinder KK, Gautam A, Mandeep Singh. Editorial-An Update on Management of Severe COVID19 Presenting with Cytokine Release Syndrome Responsible for Most Mortalities in COVID19". Acta Scientific Microbiology 2020;3(8):01-06.
4. Kulvinder KK, Gautam A, Mandeep Singh. Are We Any Closer for a Safe Vaccine to be Launched-Experience of Phase 3 Trials of Certain Vaccines withImmune Responses in COVID-19 with a 3rs Wave in Most Countries Escalating SARS-CoV2-Patients". Acta Scientific Microbiology. 2020;3(12):1-7.
5. Kulvinder Kochar Kaur,Allahbadia GN,Singh M. How can we Avoid the propagation of Neurodegenerative diseases: Aiming on Concentrating and targeting the risk factors like aging, oxidative stress, inflammation, glycation along with vascular injury –''A Systematic Review''. J Aat Physiol. 2021;2:17-29.
6. Kulvinder Kochar Kaur, Allahbadia GN, Singh M. An update on role of mitochondrial transport in etiopathogenesis & management of various CNS diseases, neurodegenerative diseases, immunometabolic diseases, cancer, viral infections inclusive of COVID 19 disease-a systematic review. J Diab Metab Disorder Control. 2021;8(3):91-103.
7. Kulvinder Kochar Kaur,Allahbadia GN,Singh M. An update on Brain organoids Generation and the Advancements made in the Context of a HumanModel of Neurological Disorders-A systematic review''. Journal of Biomedical Engineering and Medical Imaging, 2021;8(6). 31-63.
8. Kulvinder Kochar Kaur, Allahbadia GN, Singh M. Update on Genome Editing With the Utilization of CRISPR/Cas 9 System for Evaluation and Treatment of Human Diseases - A Systemic Review. Curr Trends Biomedical Eng & Biosci. 2022; 20(5): 556046.
9. Arbour N, Day R, NewcombeJ, Talbot PJ. Neuroinvasionby human respiratory Coronaviruses. J Virol 2000;74:8913-21.
10. Jacomy H, Fragaso G, Almazan GM, Mushynski WE, Talbot PJ. Human Coronavirus OC-43 infection induces chronic encephalitis leading to disabilities in BALB/Cmice. Virology. 2006;349:335-46.
11. Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S. Severe acute respiratory syndrome Coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2 . J Virol. 2008;82:7264-75.
12. Marc Desforges, Alain Le Coupanec, Philippe Dubeau, Andréanne Bourgouin, Louise Lajoie, Mathieu Dubé, Pierre J Talbot. Human Coronavirus and other respiratory viruses:underestimated opportunistic pathogens of central nervous system? Viruses. 2019;12:14.
13. Li MY,n Li L, Zhang Y, expression of the SARS-CoV2 receptor gene ACE2 in a variety of human tissues. Infect Dis Povert. 2020;9:45.
14. Singh HO, Singh A, Khan AA, Gupta V. Immune mediating molecules and pathogenesis of COVID19 associated Neurological disease. Microb Pathog. 2021;158:105023.
15. Briguglio M, Bona A, Porta M, Dell'Osso B, Pregliasco EE, Banfi G. Disentangling the hypothesis of host dysosmia and SARS-CoV2 :the bait symptom that hides

neglected Neurophysiological routes . Front Physiol. 2020;11:671.

16. Erickson MA, RheaEM, KnoppRC, BanksWA. Interactions of SARS-CoV2 with the blood brain barrier. Int J Mol Sci 2021:22:2681.
17. Wang C, Zhang M, Garcia G, Tian E, CuiQ, Chen X, et al. Apo E- isoforms dependent SARS-CoV2 neurotropism andcellularresponse. Cell Stem Cell. 2021;28:331-45.e5.
18. Zhou Y, XuJ, Hou Y, Leverenz JB, Kallianpur A, Mehra R, et al. Network medicine, links SARS-CoV2 / COVID-19 infection to brain micro vascular injury and Neuro inflammation in dementia like cognitive impairment. Alzheimers Res Ther. 2021;13:110.
19. Achar A, Ghosh C. COVID-19 associated disorders :the potential routes of CNS invasion and blood brain Neurological ion network medicine relevance . Cells. 2020;9:2360.
20. McCray PB, Pewe L, Wohlford Lenane C, Hickey M, Manzel L, Shi L, et al. Lethal infection of K18-hACE2mice infected with severe acuterespiratory distress syndrome Coronavirus . J Virol. 2007;81:813-21.
21. Barnett EM, Cassell MD, Perlman S. Two neurotropic viruses, herpes simplex virus type1 and mouse hepatitis virus spread along different neural pathways from the main olfactory bulb. Neuroscience. 1993;57:1007.
22. Mullol J, Alobid L, Martinez, Sanchez F, Isquierdo-Dominquez A, Marin C, KlimekL, et al. The loss of smell and taste in the COVID19 outreak:a tale of many countries. Curr Allergy Asthma Rep. 2020; 20;9:61.
23. Rebholz H, Braun RJ, Ladage D, Knoll W, Kleber C, Hassell AW. Loss of olfactory function early indicatore, COVID19, other viral infections and degenerative disorders. Front Neurol 2020;11:569333.
24. Desai M, Oppenheimer J. The importance of considering olfactory dysfunction during COVID-19 pandemic and in Clinical practice. J Allergy Clin Immunol Pract. 2021;9:7-12.
25. Lechien JR, Chiesa Estomba CM, de Siati DR, Horoi M, leBonSD, et al. Olfactory and Gustatory dysfunctions as a Clinical presentation of mild to moderate forms of Coronavirus disease (COVID19):A multi center European study. Eur Arch Oto-Rhino-Laryngol. 2020;277:2251-61.
26. Kandemeri SG, Altundag A, Yildirim D, Teckan Sanli DE, Saatci O. Olfactory bulb MRI and paranasal sinus CT findings in persistent COVID19 anosmia.Acad Radiol. 2021;28:28-35.
27. Porta-Etessam J, Nunez Gil IJ, Gonzalez Garcia N, Fernandez- Perez C, Viana-Llamas MS, Eid CM, et al. COVID19 anosmia and Gustatory symptoms as a prognostic factor: a sub analysis pf the HOPE-COVID19(Health Outcome Predictive Evaluation for COVID19)registry . Infection. 2021;49:677-84.
28. PougaI. Encephalitic syndrome and anosmia in COVID19:do these Clinical presentations really reflect SARS-CoV2 neurotropism ?a theory based on the review of 25 COVID19 cases. J Med Virol. 2021;93:550-8.
29. Rhea EM, Logsdon AF, Hansen KM, Williams LM, Reed MJ, Baumann KK, et al. The S1 protein of SARS-CoV2 crosses the blood brain barrier in mice. Nat Neurosc. 2021;24:368-78.
30. Eldeeb MA, Hussain FS, Siddiqi ZA. COVID19 Infection may increase the risk of Parkinsonism-remember the Spanish flu? Cytokine Growth Factor Rev. 2020;54:6-7.
31. Pajo AT, Espiritu AI, Apor ADAO, Jamra RDG. Neuropathologic Findings of patients with COVID19:a systematic review . Neurol Sc 2021;42:1255-66.
32. Boroujeni ME, Simani L, Bluyssen HAR, Samadikhah HR, Zamanlui Benisi S, Hassani S, et al. Inflammatory response leads to neuronal death in human post mortem Cerebral cortex in patients with COVID19.ACS Chem Neurosc. 2020;92:699-702.
33. Paniz MondolfiA, Bryce C, Grimes Z, Gordon RE, ReidY JA, Lednicky J, et al. Central nervous system involvement by severe acuterespiratory distress syndrome Coronavirus 2(SARS-CoV2). J Med Virol. 2021;12:660087.

34. Pacheco Herrero M, Soto Rajjas LO, Harrington CR, Flores - Martinez YM, Villegas-Rojas MM,etal. Elucidating the pathological mechanisms of SARS-CoV2 Infection. Front Neurol. 2021;12:660087.
35. Poloni TE, Medici V, Moretti M, Vissona SD, Cirrincione A, Carlos AF, et al. COVID19 related Neuropathology and microglial activation in elderly with and without dementia. Brain Pathol. 2021;31:e12997.
36. Serrano GE, Waiker JE, Arce R, Glass MJ, Vargas D, Sue LI, et al. Mapping of SARS-CoV2 brain invasion and histopathology in COVID19disease. medRxiv 2021,the preprint server for health sciences.
37. Garcia MA, Barreras BV, Lewis A, Pinnila G, Sokoll LJ, Kickler T, et al. Cerebrospinal fluid in COVID19 neurological complications . Neuroaxonal damage, anti SARS-CoV2 antibodies but no evidence of no cytokine storm. J Cell Neurol Sci. 2021;427:117517.
38. Sun B, Tang N, Peluso MJ, Iyer NS, Torres L, Donatelli JL, et al. Characterization and biomarker analysis of post covid-19 complications and Neurological manifestations. Cells. 2021;10:386.
39. Alexopoulous H, Magira E, Bitzogli K, Kafasi N, Vlachoyiannopoulous P, Tziofaus A, et al. Anti SARS-CoV2 antibodies in the CSF, blood brain barrier dysfunction, and neurological outcomes: status in 8 stuporose and comatose patients. Neurol Neuroimmunol Neuroinflamm. 2020;7:e893.
40. Hosp J, Dressing A, Blazhenets G, Bormann T, Rau A, Schwabenland M, et al. Cognitive impairment and altered cerebral glucose metabolism in the subacute stage of COVID19. Brain 2021;144- 1263-76.
41. Luis MB, Liguori NF, Lopez PA, Alonso R. SARS-CoV2 RNA detection in cerebrospinal fluid: presentation of two cases and review of literature. Brain Behave iimmune Health. 2021;15:100282.
42. Garcia MA,Barreras BV,LewisA,Pinnila G,Sokoll LJ,Kickler T,etal. cerebrospinal fluid in COVID19 neurological complications: no cytokine storm or Neuroinflammation. medRxiv 2021,the preprint server for health sciences.
43. Hoffman LA,Vilensky JA. Encephalitis lethargica: 100years after the epidemic. Brain 2017;140:- 2246-51.
44. Meng L, Shen L, Ji HF. Impact of infection on risk of Parkinson's disease: a quantitative assessment of case control and cohort studies. J Neuro Virology. 2019;25:221-8.
45. Sadasivan S, Zanin M, O'Brien K, Schultz Cherry S, Smeyne RJ. Induction of microglial activaafter injection with non neurotropic A/CA/04/2009 H1NI1 Influenza virus.PL oS ONE2011;6:e124047.
46. Jang H, Boltz D, Sturmz-Ramirez K, Shepherd KR, JiaoY, Webster R, et al. Highly pathogenic H5NI1 Influenza virus can enter the central nervous system and Induce Neuroinflammation and Neurodegeneration. Proc NatlAcad Sci USA. 2009;106:14063-8.
47. Rohn TT, Catlin LW. Immunlocalization of Influenza virus and markers of inflammation in the human Parkinson's disease brain. PL oS ONE. 2011;6:e20495.
48. Bu XL, Wang X, Xiang Y, Shen LL, Wang QH, Liu YH, et al. The association between infectious burden and Parkinson'sdisease: A case control study. Parkinsonism Relat Disord. 2015;21:-877-81.
49. Limphaibool N, Iwanowsky P, Holstad MJV, Kobylarek Dozubsky W. Infectious etiologies of Parkinsonism: pathomechanisms and Clinical implications. Front Neurol. 2019;10:659.
50. Lin WY, Lin MS, Weng YH, Yeh TH, Lin YS, Fong PY, et al. Association of antiviral therapy with risk of Parkinson'sdisease in patients with chronic Hepatitis C virus infection. JAMA Neurol. 2019;76:1019-27.
51. Tzeng NS, Chung CH, Lin FH, Chiang CP, Yeh CB, Huang SY, et al. Anti herpetic medications and reduced risk of dementia in herpes simplex virus infections-a nationwide population based cohort study in Taiwan. Neurotherapeutics. 2018;15:417-29.
52. Cocros NM, Svensson E, Szepligti SK, Vestergaard SV, Sze ntkuti P, Thomsen RW, et al. Long term riskof Parkinson'sdisease following Influenza and other infections. JAMA Neurol. 2021 ;78:1461-70.

53. Murgod UA, Methane UB, Ravi V, Radhesh S, Desai A. Persistent movement disorders following Japanese encephalitis. Neurology. 2001;57:2313-5.
54. Beatman EL, Massey A, Shives KD, Burrack KS, Chamaniam M, Morrison TE. Alpha synuclein expression restricts RNA viral infections in the brain. J Virol. 2016;90:2767-82.
55. Wainberg M, Luquez T, Koelle DM, Readhead B, Johnston C, Darvas M, et al. The viral hypothesis: how herpes virus may contribute to Alzheimer'sdisease. Mol Psychiatry. 2021 ;26(10):5476-80.
56. Duarte LF, Farias MA, Alvarez DM, Bueno SM, Riedel CA, Gonzalez PA. Herpes simplex virustype 1 infection of the central nervous system: insights into proposed inter relationships with Neurodegenerative disorders. Front Cell Neurol. 2019;13:46.
57. Sulzer D, Alcalay RN, Garretti F, Cote L, Kanter E, Agin Liebes J, Liong C, et al. T cells from patients with Parkinson's disease recognize α-synuclein peptides. Nature. 2017;546:656-61.
58. Sommer A, Maxreiter F, Krach F, Fadler T, Grosch J, Maroni M, et al. Th17 Induce neuronal cell death in a human iPSCs based model of Parkinson's disease. Cell Stem Cell. 2018;23:123-31.e6.
59. Gate D, Tapp E, Leventhal O, Shahid M, Nonninger TJ, Yang AC, et al. CD4+ T cells contribute to Neurodegeneration in Lewy body dementia. Science. 2021;374:868-74.
60. Idrees D, Kumar V. SARS-CoV2 spike protein interactions with amyloidogenic proteins: potential clues to Neurodegeneration. Biochem Biophys Res Commun. 2021;554:94-8.
61. Liu S, Hossinger A, Heumuller S, Hornberger A, Buravlova O, Konstantoulea K, et al. Highly efficient intercellular spreading of protein misfolding mediating by viral ligand receptor interactions. Nat Commun. 2021;12:5739.
62. Lippi A, Domingues R, Setz C, Outeiro TF, Krisko A. SARS-CoV2 :at the crossroads between aging and Neurodegeneration. Mov Disord. 2020;35:716-20.
63. Singh K, Chen YC, Judy JT, Seifuddin F, Tunk I, Piroznia M. Networkanalysis and transcriptoming profiling identify autophagic and mitochondrial dysfunctionsin SARS-CoV2 infection. bioRevb. 20120.
64. Sfera A, Osoria C, Maguire G, Rahman L, Afzaal J, Cummings M, Maldonando JC. COVID19 Ferrosenescence and neurodegeneration,a minireview. Prog NeuroPsychopharmacol Biol Psychiatry. 2021;109:110230.
65. Fishman PS, Gass JS, Swoveland PT, Lavi E, Highkin MK, Weiss SR. Infection of the basal ganglia bymurine Coronavirus. Science. 1985;229:877-9.
66. Fazzini E, Fleming J, Fahn S. Cerebrospinal fluid antibodies to Corona virus in patients with Parkinson's disease. Movement Disordorders. 1992;7:153.
67. Merello M, Bhatia KP, Obeso JA. SARS-CoV2 and the risk of Parkinson's disease: facts and fantasy . Lancet Neurol. 2021;20:94-5.
68. Morassi M, Palmerini F, Nici S, Magni E, Savelli G, Guerra UP, et al. SARS-CoV2 related encephalitis with prominent Parkinsonism: Clinical and FDG-PET correlates in two patients . J Neurol. 2021;268:3980-7.
69. Brundin P, Nath A, Beckham JD. Is COVID19 a perfect storm for Parkinson's disease? Trends Neurosci. 2021;43:931-3.
70. Chen H, O'Reilly FJ, Schwarschild MA, Ascherio A. Peripheral inflammatory biomarkers and risk of Parkinson's disease. AmJ Epidemiol. 2008;167:90-5.
71. Pistarini C, Fiabane E, Houdayer E, Vassalo C, Manera M, Alemanno F. Cognitive and emotional disturbance dueto COVID19:an exploratory study In the rehabilitation setting. Front Neurol. 2021;12:643646.
72. Yang L, Cornell W, Kim MT, Nair M, Harschnitz O, Wang P, et al. SARS-CoV2 infection causes dopaminergic neurons Senescence. Res Sq 2021.
73. Ramani A, Muller L, Ostermann PN, Gabriel E, Abida-Islam P, Muller Schifmann A, et al. SARS-CoV2 targets neurons of3D human organoids. EMBO J 2020;39:e106230.
74. Ghosh A, Roy A, Liu X, Kordower JH, Mufson EJ, Hartley DM, et al. Selective inhibition of NFκB

activation prevents dopaminergic neuronal loss in a mouse model of Parkinson's disease. Proc NatlAcad Sci USA. 2007;104:18754-9.

75. Chaudhary ZL, Klenja D, Janjua N, Cami-Kobeci G, Ahmed BY. COVID19 and Parkinson's disease: shared inflammatory pathways under Oxidative stress. Brain Sci. 2020;10:807.
76. Milsted A, Barnaf BP, Ransohoff RM, Bridget Brosnihan K, Ferrario CM. Astrocytecultures derived from human braintissue express angiotensinogen mRNA(gene expression / Renin-angiotensin –System/ central nervous system/ angiotensin. Proc NatlAcad Sci USA. 1990;87:5720-3.
77. Labandeira-Garcia JL, Rodriques-Pallares J, Dominguez-Meijede A, Valanzuela R, Villar Cheda B, Rodriques -Perez AI. Dopamine Angiotensin interactions in the basal ganglia and their relevance for Parkinson'sdisease. Mov Disord 2013;28:1337-42.
78. Soscia SJ, Kirby JE, Washicosky KJ, Tucker SM, Ingelsson M, Hyman B, et al. The Alzheimer'sdisease associated amyloid β protein is an antimicrobial peptide. PL oS ONE. 2010;5:e9505.
79. Marreiros R, Muller Schifmann A, Trossbach SV, Prikulis J, Hansch S, et al. Disruptionof cellular proteostasisby H1N1A Influenza virus causes α-synuclein aggregation. Proc NatlAcad Sci USA. 2020;117:6741-51.
80. Baraak H, del Tredici K. Neuropathological staging of brain pathology sporadic Parkinson'sdisease :separating wheat from the chaff. J Parkinson's Dis. 2017;7:S73-S87.
81. Romano S, Savva GM, Bedarf JR, Charles IG, Hildebrand F, Narbad A. Meta-analysis of the Parkinson'sdisease gut microbiome suggests alterations linked to intestinal inflammation.npj Parkinson's Dis. 2021;7:27.
82. Eifenberger M, Grabherr F, Mayr L, Schwaerzler J, Nairz M, Seifert M, et al. Fecal calprotectin indicates intestinal inflammation in COVID19. Gut 2020;69:1543-4.
83. Xiao F, Tang M, Zheng X, Liu Y, Li X, Shen H. Evidence for gastrointestinal infection of SARS-CoV2 . Gastroenterology 2020;158:1831-3.e3.
84. Anghelescu BA-M, Bruno V, Martino D, Roach P. Effects of the COVID19 pandemic on Parkinson's disease :a Single centered qualitative study. Can J Neurol Sci. 2021;12:1-13.
85. Estrada E. Cascading from SARS-CoV2 to Parkinson's disease through protein - protein interactions. Viruses 2021;13:897.
86. Vavogios GD. Human Corona viruses in idiopathic Parkinson's disease: implications of SARS-CoV2 modulationn of the host's Transcriptome. Infect Genet Evol. 2021;89:104733.
87. Rosen B, Kurtishi A, Vasquez-Jimenez GR, Moller SG. The intersection of Parkinson's disease, viral infections, and COVID19. Mol Neurobiol 2021;58:4477-86.
88. Ait Wahmane S, Achbani A, Ouhaz Z, Elatiqi M, Belmouden A, Nejmeddine M. The possible protective role of α-synuclein against severe acute respiratory distress syndrome against severe Coronavirus2 infections in patients with Parkinson'sdisease. Mov Disord. 2020;35:1293-4.
89. Malpetti M, Pasamonti L, Jones PS, Street D, Rittman D, Fryer TD, et al. Neuroinflammation predicts disease progression, in progressive supranuclear palsy. JNeurol Neurosurg Psychiatry. 2021;92:769-75.
90. Palleis C, Sauerbeck J, Beyer L, Harris S, Schmitt J, Morenas- Rodriques E, et al. *In vivo* assessmentof Neuroinflammation in 4 repeat tauropathies. Mov Disord. 2021;36:883-94.
91. Del Brutto OH, Wu S, Mera RM, Costa AF, Recalde BY, Issa NP. Cognitive decline among individuals with history of mild symptomatic SARS-CoV2 infections: a longitudinal prospective study nested to a population cohort. Eur JNeurol 2021;28:3245-53.
92. Jaywant A,Vanderlind WM, Alexopoulous GS, Fridman CB, Perlis RH, Gunning FM. Frequency and profile of Objective Cognitive deficits in hospitalized patients recovering from COVID19. Neuropsychopharmacology. 2021;46:2235-40.

93. Rogers JP, Cherney E, Oliver D, Pollak TA, McGuire P, Fusar Poli P, et al. Psychiatric and neuropsychiatric presentations associated with severe Coronavirus2 infections: a systematic review and meta-analysis with comparison to the COVID19 pandemic. Lancet Psychiatry. 2020;7:611-27.
94. Versace V, Sebastianelli L, Ferrazzoli D, Romanello R, Ortelli P, Saltuari L, et al. Intracortical GABAergic dysfunction in patients with fatigue and dysexecutive syndrome after COVID19. Clin Neurophysiological 2021;132:1138-43.
95. Xia X, Wang Y, Zheng J. COVID19 and Alzheimer's disease: how one crisis worsens the other? Transl Neurodegn 2021;10:15.
96. Mikkelsen ME, Christie J, Lanken PN, Biester RC, Thomson BT, Ballmy SL, et al. The adult respiratory distress syndrome cognitive outcome study: long term neuropsychological functions: in survivors of acute lung injury. AmJ Respir Crit Care Med. 2012;185:1307-15.
97. Rangon CM, Krantic S, Moyse A, Fougere B. The vagal autonomic pathway of COVID19 at the cross road of Alzheimer's disease and aging:a review of knowledge. J Alzheimer's Dis Rep. 2020;4:537-51.
98. Vrillon A, Mhanna E, Aveneau C, Lebozec M, Grosset L, Nankam D, et al. COVID19 in adults with dementia: Clinical features andrisk factors of mortality:a Clinical cohort study on 125 patients. Alzheimer's Res Ther. 2021;13:77.
99. Lee S, Viqar F, Zimmerman ME, Narkhede A, Tosto G, Benzinger TLS, et al. White matter hyper intensities are a core feature of Alzheimer'sdisease : evidence from the dominantly inherited Alzheimer'sdisease .Ann Neurol. 2016;79:929-39.
100. Kuo CL, Pilling LC, Atkins JL, Masoli JAH, Delgado J, Kuchel GA, Menzer D. APOEe4 genotype predicts severe COVID19 in the UKBiobank community cohort. J Gerontol Ser A Biol Sci Med Sci. 2020;75:2231-2.
101. Chen X, Zhao B, Qu Y, Chen Y, Xiong J, Feng Y, et al. Detectable serum SARS-CoV2 (RNAaemia) is closely correlated with drastically elevated interleukin-6(IL-6) level in Critically ill COVID19 patients. Clin Infect Dis. 2020;71:1937-42.
102. Kaczmarczyk R, Tejera D, Simon BJ, Heneka MT. Microglia modulation through external vagal nerve stimulation in a murine model of Alzheimer's disease. J Neurochem. 2018;146:76-85.
103. Naughton SX, Raval U, Pasinetti GM. Potential novel role of COVID19 in Alzheimer's disease. J Alzheimer's Dis 2020;76:21-5.
104. Garcia Azorin D, Secher KM, Newton CR, Okubadejo NU, Pilotto A, Saylor D, et al. Disruptions of neurological servicesits causes and mitigation strategies during COVID19:a global Review. JNeurol. 2021;268:3947-60.
105. Fearon C, Fasson A. Parkinson's disease and the COVID19 pandemic. J Parkinson's Dis. 2021;11:431-44.
106. Leta V, Rodriques Volante M, Abundes A, Rukavina K, Teo JT, Falup PrecariruC, et al. Parkinson'sdisease and post COVID19 syndrome:The Parkinson's long COVID19 spectrum. Mov Disord 2021;36:1287-9.
107. Balci B, Aktar B, Buran S, Tas M, Donmez-Colakoglu B. Impact of the COVID19 pandemic on physical activity, anxiety and depression in patients with Parkinson's disease. Int J Rehab Res. 2021; 44:173- 6.
108. Helmich R C, Bloem BR. The Impact of the COVID19 pandemic on Parkinson's disease: hidden sorrows and emerging opportunities. J Parkinson's Dis. 2021;10:351-4.
109. Cavallieri F, Sreci F, Fioravanti V, Toschi G, Rispoveli Antonelli F, et al. Parkinson's disease patients needs during the COVID19 pandemic in a red zone:a framework analysis of open ended survey questions. Eur J Neurol. 2021;28:3254-62.
110. Vila-Vicosa D, Clemente A, Pona Ferreira F, Leitao M, Bocau-Machado R, Kaupilla LA, et al. Unsupervised walking activity assessment reveals COVID19 Impact on Parkinson's disease patients. Mov Disord Off J Mov Disord Soc. 2021;38:531-2.
111. Kumar N, Gupta R, Kumar H, Mehta S, RajanR, Kumar D, et al. Impact of home confinement during the

COVID19 pandemic on sleep parameters in Parkinson's disease. Sleep Med 2021;77:15-22.

112. Xia Y, Kuo L, Zhang G, Han C, Hu J, Wan F, et al. Investigation on sleep and mental health of patients with Parkinson's disease during the Coronavirus disease 2019 pandemic. Sleep Med. 2020;75:428-33.
113. Klietz M, von Eichel H, Schnur T, Staege S, Hoglinger GU, Wegner F, et al, One year trajectory of caregiver burden in Parkinson'sdisease and analysis of gender specific aspects. Brain Sci 2021;11:295.
114. Montanaro E, Artusi CA, Rosano C, Boschetto C, Imbalzano G, Romagnolo A, et al. Anxiety depression and worries in advanced Parkinson's disease during COVID19 pandemic. JNeurol Sci 2021;1-8.
115. Hu C, Chen C, Dong XP. Impact of COVID19 pandemic in patients with Neurodegenerative diseases. Front Aging Neurosci 2021;13:664965.
116. Vignatelli L, Zanesini C, Belotti LMB, Baldin E, Bonavina G, Calendra-Buonaura G, et al. Risk of hospitalization and death in people with Parkinson's disease or Parkinsonism . Mov Disord Off J Mov Disord Soc. 2021;36:1-10.
117. Huber MK, Raichle C, Lingor P, Synofzik M, Borgmann S, Erber J, et al. Outcome of SARS-CoV2 infections in patients with Neurodegenerative disease sin theLEOSS cohort. Mov Disord 2021;36:791-3.
118. Fasano A, Cereda E, Banchella M, Cassani E, Ferri V, Zachinelli AL, et al. COVID19 in Parkinson's disease patients livi ng in Lombardy, Italy. Mov Disord. 2020;35:1089-93.
119. Kamel WA, Kamel ML, Ahlasawi A, Elmasry S, Al Hamdan F, Al Hashel JY. Effect of preexposure use of amantadine on COVID19 infection in patients with Parkinson's diseaseor multiple sclerosis. Front Neurol 2021;12:643646.
120. Artusi CA, Romagnolo A, Ledda C, ZibettiM, Rizzone MG, Montanaro E, et al . COVID19 and Parkinson's disease: what do we know so far? J Parkinson's Dis 2021;11:445-54.
121. Zhang Q, Schultz JL, Altridge GM, Simmering JE, Narayanan NS. Coronavirus disease 2019 case fatality and Parkinson's disease. Mov Disord. 2020;35:1914-5.
122. Scherbaum R, Kwon EH, Richter D, Bartig D, Gold R, Krogias C, et al. Clinical profiles and mortality of COVID-19 in patients with Parkinson's disease in Germany. Mov Disord 2021;36:1049-57.
123. Hainque E, Grabli D. Rapid worsening in Parkinson's disease might hide COVID19 infection. Parkinsonism Relat Disord. 2020;75:126-7.
124. Goerttler T, Hae-Kwan E, Fleischer M, Stettner M, Tonges L, Klebe S. SARS-CoV-2, COVID-19 and Parkinson's Disease-Many Issues Need to Be Clarified-A Critical Review. Brain Sci 2022;12:486.

Contusm International Publications

https://ijcasereports.com/