



Cognitive decline following acute viral infections: literature review and projections for post-COVID-19

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Abstract

Recently, much attention has been drawn to the importance of the impact of infectious disease on human cognition. Several theories have been proposed, to explain the cognitive decline following an infection as well as to understand better the pathogenesis of human dementia, especially Alzheimer's disease. This article aims to review the state of the art regarding the knowledge about the impact of acute viral infections on human cognition, laying a foundation to explore the possible cognitive decline followed coronavirus disease 2019 (COVID-19). To reach this goal, we conducted a narrative review systematizing six acute viral infections as well as the current knowledge about COVID-19 and its impact on human cognition. Recent findings suggest probable short- and long-term COVID-19 impacts in cognition, even in asymptomatic individuals, which could be accounted for by direct and indirect pathways to brain dysfunction. Understanding this scenario might help clinicians and health leaders to deal better with a wave of neuropsychiatric issues that may arise following COVID-19 pandemic as well as with other acute viral infections, to alleviate the cognitive sequelae of these infections around the world.

Keywords Cognition · Alzheimer's disease · Virus · Dementia · COVID-19 · Prevention

Introduction

Cognitive impairment is a vital healthcare problem worldwide. Population studies have shown that 3–19% of the population older than 65 years meet criteria for mild cognitive impairment (MCI) [1, 2]. Of these, more than 50% will develop dementia [2]. Global prevalence of dementia in the population is 1.3%, and 7.3% in people aged 65 years or more [3], which is similar to those found in Latin American

population [4]. Many studies have shown a direct influence of viral infections on cognition, especially in the development of MCI and dementia [5–7]. The high prevalence and the overlap of both conditions underscore the importance of a better understanding of the role of viral infections in the pathogenesis of dementia [8, 9].

Viral infections significantly impact world's global burden of medical and neurological diseases [8]. In the last decades, the role of viral infections in cognitive impairment following has been widely discussed [5]. Viruses, such as herpes viruses, cytomegalovirus, human immunodeficiency virus (HIV), Varicella zoster virus (VZV), Epstein–Barr virus (EBV), and Hepatitis C virus, have been implicated in Alzheimer's disease pathogenesis [7, 10]. Mechanisms underlying viral pathogenesis in these conditions may include a direct viral effect or indirect mechanisms, such as inflammation, epigenetic changes, and hypercoagulable changes, that may impact on brain structure and function in healthy or in cognitively impaired individuals [6, 11–15]. Previous reviews have also addressed this topic; however, most of them are not specific to acute viral infections [6],

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restricted to few viral infections (e.g. Herpes virus) [7] or letter to editors [5].

In this context, emerging infectious diseases, especially those affecting the population on a pandemic scale, should be monitored for potential neuropsychiatric compromise. This may be the case of coronavirus disease 2019 (COVID-19), which currently challenges physicians and health care professionals not only for its high mortality and severity of clinical manifestations, but also for emergence of atypical and unexpected clinical presentations [16], such as cognitive impairment [17]. Some experts worldwide [18], including those from the Alzheimer's Association, have been interested in studying this potential association, reviewing the most updated evidence towards this topic and proposing a cross-cultural prospective study to assess individuals reporting cognitive impairment and other neuropsychiatric complaints [19]. However, there is still a need of further theoretical studies, especially using a multi-specialist approach, to discuss further this matter and guide for future interventional studies.

To address this matter, we conducted a comprehensive literature review with different specialists (neurologists, geriatrists, psychiatrists, neuropsychologists), to address the available studies that investigated the occurrence of cognitive decline following the most prevalent acute viral infections. Moreover, understanding about the pathophysiology of the cognitive impairment following other viral infections will help to better understand the emergence of neuro-cognitive symptoms among COVID-19 survivors. Post-COVID cognitive impairment may represent an important clinical feature of the disease, and may impose an additional and long-lasting burden, especially psychiatric and cognitive issues, particularly among older adults. Recognizing cognitive impairment following COVID-19 may be essential to promote preventive and therapeutic interventions and help clinicians worldwide to identify and treat this condition. This narrative review aims to bridge this gap, presenting the literature about the impact of viral infections on cognition, as well as to develop a theoretical framework on how COVID-19 impacts in the CNS function and may cause cognitive impairment.

Methods

We conducted a narrative review of literature following international guidelines for writing narrative reviews [20, 21]. First, two authors have searched three databases (PubMed, Scielo and EMBASE) using the following keywords: “Cognition”, “Cognitive Impairment”, “Cognitive Decline”, “Dementia”, “Alzheimer's Disease”, “Virus”, “Acute”, “Viral Infection”, “Infection”, and “Infectious Disease”, with restriction of title, abstract and keyword. We selected

additional disease-specific parameters (“Herpes simplex type 1”, “varicella-zoster”, “West Nile virus”, “Influenzae”, “Japanese encephalitis”, “aseptic meningitis”, “Acute respiratory distress syndrome”), adding the name of the parameter to the Boolean search. Selected articles were also searched for references. We accepted only articles in English, Spanish, Italian, and Portuguese. Selected articles were discussed with all authors and then included in the review.

Pathophysiology and types of the cognitive impairment following viral infections

First, it is important to give clear definitions about cognitive decline (or cognitive impairment), mild cognitive impairment, dementia and Alzheimer's disease, respectively. Cognitive decline can be understood as the loss of cognitive performance. It can be linear and natural or can have a non-linear and accelerated characteristic of loss [22]. The latter, when not impact activities of daily life, is called mild cognitive impairment (MCI), whereas dementia notably interferes on daily life [2]. The most common cause of dementia is the Alzheimer's disease, which can be defined as a chronic neurodegenerative disorder, characterized by the accumulation in brain of amyloid- β (A β) and tau protein [23]. Cognitive impairment may be caused by viral infections associated with direct invasion of the central nervous system [11, 24], or as an indirect effect of systemic infections not typically causing CNS infection (e.g. cytokine storm, neuro-inflammation, hypercoagulability) [11, 24].

Moreover, encephalitis is defined as an inflammation of the brain parenchyma associated with neurologic dysfunction, which usually manifests clinically with seizures, encephalopathy, focal neurologic signs and symptoms. In 2013, the International Encephalitis Consortium issued standardized and now widely case definitions for encephalitis. Diagnosing encephalitis requires demonstration of altered mental status decreased or altered level of consciousness, lethargy or personality change) lasting > 24 h, combined with at least two minor criteria (fever, new-onset seizures, focal signs, CSF pleocytosis, parenchymal abnormalities on neuroimaging, or typical electroencephalogram findings) for possible encephalitis, and three minor criteria for probable encephalitis [25]. For aseptic meningitis, Brighton Collaboration case definitions are widely used. Diagnosing aseptic meningitis requires clinical evidence of meningitis (fever, headache, vomiting, nuchal rigidity), and CSF pleocytosis, and negative CSF culture [26]. Distinguishing between meningitis and encephalitis is often elusive, given the shared disease mechanisms and clinical overlap. To avoid such confusion, the more encompassing term “meningoencephalitis” is frequently used interchangeably with meningitis and encephalitis.

Below, we will summarize the most important findings regarding six viruses that causes acute infections and its impact on cognition.

Herpes simplex virus type 1

Molecular biology and epidemiology

Herpes simplex virus type 1 (HSV-1) is a double-stranded DNA virus of the herpesviridae family. It is the leading cause of acute infectious encephalitis worldwide [27–29]. The incidence of HSVE is estimated to be between 2 and 4 cases/1,000,000, without clear regional differences [30, 31].

Mechanisms of infection

HSV primary infection involves skin or mucosae. Following primary infection, the virus infects sensory neurons and, ultimately, the dorsal root ganglia, via axonal transport. After prolonged latent infection, the virus may access the central nervous system by retrograde transport through trigeminal or olfactory nerves [32]. The predilection for involvement of mesiotemporal and limbic cortices may be explained by the intense connectivity between the olfactory nerves and the limbic system [33].

Clinical manifestation

Acute herpes simplex encephalitis presents commonly with prodromal symptoms, such as fever and respiratory symptoms, which progress over several days to encephalopathy, focal neurological signs and seizures [32, 34]. Neuroimaging shows characteristic but variable degrees of restricted diffusion, T2/FLAIR hyper-intensities and contrast enhancement in the mesial temporal lobes, orbito-frontal, insular and anterior cingulate cortices, frequently bilateral and asymmetrical [32, 34]. Typical CSF findings include mild-to-moderate pleocytosis (10–200 WBC/mm³), mildly elevated protein (50–100 mg/dL) and normal glucose [32].

Impacts on cognition

Herpesviridae viruses can be implicated in late-onset Alzheimer's disease pathogenesis [35, 36], probably due to the increased amyloid- β amyloidosis [37]. Early reports from the pre-acyclovir era describe severe anterograde amnesia due to bilateral hippocampal damage in surviving HSV-1 patients [38]. A few patients followed longitudinally over long periods [39–46], display persistent severe anterograde and retrograde amnesia, with relatively preserved remote memories, the hallmark of bilateral hippocampal lesions. The severity of retrograde amnesia in HSV-1 patients is possibly associated with greater involvement of temporal

lobe structures, including the temporal poles and temporal neocortical regions [43].

Memory deficit severity correlates with the extent of medial temporal lobe involvement and is the most important late finding in HSV encephalitis [47]. Bilateral lesions are associated with more profound cognitive deficits, involving semantic memory impairment and visual agnosia [42, 48]. Executive dysfunction, possibly due to orbito-frontal and anterior cingulate cortices damage is also recognized in HSV-1 encephalitis [49].

Although HSV-1 survivors may show improved cognition over time, cognitive impairment is an enduring long-term consequence of brain damage. Severe memory impairment is recognized in 40–58% of patients one year after the encephalitis [50–52], and 80% of patients display persistent mild cognitive deficits three years after the acute episode [53]. The advent of acyclovir, in the late 1980s, considerably modified the prognosis of HSV-1 encephalitis [54–56]. Mortality rates have dropped below 20% [34, 57]. Cognitive impairment, however, remains very common in acyclovir-treated patients [52].

Varicella zoster virus

Molecular biology and epidemiology

Varicella zoster virus (VZV) is a ubiquitous exclusively human DNA virus of the herpesviridae family and is the second cause of encephalitis worldwide [27, 29, 58].

Mechanisms of infection

Following primary infection, the VZV remains latent in cranial, dorsal root, and autonomic ganglia [59]. Iatrogenic immunosuppression and advanced age are associated with decreased cell-mediated immunity, which leads to VZV reactivation and neurological complications [60]. VZV reactivation shares many mechanisms with HSV-1 reactivation, and retrograde axonal transport within sensory neurons plays an important role [61].

Clinical manifestation

VZV can cause miscellaneous central nervous system diseases, including as meningitis, encephalitis, myelitis and CNS vasculopathy which frequently overlap [60]. Most frequently, VZV reactivates as shingles, and the infection is limited to the peripheral nervous system, with rash resolution over a few weeks. Occasionally, especially in immunocompromised patients, meningoencephalitis occurs. Clinical presentation is similar to other encephalitis syndromes, with varying degrees of encephalopathy, seizures, and headache. CSF studies show the typical profile

of viral meningoencephalitis, with 50–300 WBC/mm³, and 40–150 mg/dL of protein [62, 63]. In encephalitis cases, neuroimaging shows encephalitic abnormalities nearly as frequently as signs of intracranial vasculitis [62].

Impacts on cognition

Studies assessing prognosis using hard endpoints in the post-acyclovir era showed neurological impairment in 20–60% of patients upon hospital discharge [62–64], 55% after one month, 51% after three months and 71% after one year [62, 65] after the acute episode. Recent attention has been drawn to potential long-term effects of herpes virus infection on cognition in the absence of an acute neurological syndrome. Viral presence in the CNS may interfere with pathogenic mechanisms related to neurodegenerative diseases, such as Alzheimer's disease (AD) [7, 10]. According to the 'viral hypothesis of AD', this interaction may be non-specifically associated with up-regulation of inflammatory responses and oxidative stress, which are secondary, but relevant components of the amyloid cascade. This interaction may also operate through a specific mechanism within the core pathogenesis, hastening amyloid overproduction [10, 12].

Japanese encephalitis

Molecular biology and epidemiology

Japanese encephalitis (JE) is the most common cause of encephalitis in Asia, affecting mainly children. Adult cases are increasingly reported [66]. JE is also a relevant cause of encephalitis in the western pacific, and JE cases have also been reported in Australia [67]. The disease is caused by the Japanese Encephalitis virus (JEV), a mosquito-borne single-stranded RNA virus of the flaviviridae family. The disease is usually transmitted to humans following the pig–mosquito–human route [68].

Mechanisms of infection

Following subcutaneous inoculation, the JE virus infects various parts of the brain, suggesting a hematological route of infection, which could be explained by infection of endothelial cells and subsequent transcellular transport into the brain parenchyma, and paracellular leakage through damaged blood–brain barrier or blood–CSF barrier [69].

Clinical manifestation

Only one in 25 to one in 1000 infections are symptomatic [70]. Patients typically present with fever and encephalopathy, often associated with seizures and moderate CSF

pleocytosis. Neuroimaging may reveal specific abnormalities in the thalami in 22% of cases [71].

Impacts on cognition

Around 45–64% of survivors show neurological sequelae on hospital discharge [72–74]. In a Chinese retrospective series of 50 JE patients [66], 12% died during hospital admission, 75% had significant functional limitations upon discharge, and 39% of survivors had major limitations after 18 months.

These findings are in agreement with an early study conducted in Japan that found that 29% of patients had “detectable neurological sequelae” one year after the encephalitis episode [75], as well as with recent studies conducted in India and Japan, showing that 100% of patients had neurologic deficits on hospital discharge [76], 44% of patients had at least one neurological CNS sequel one to two years post encephalitis [74]. Cognitive deficits, especially intellectual disability and memory loss have been presented both in children and adults [72, 74] as well as memory learning in rats [77].

West Nile virus encephalitis

Molecular biology and epidemiology

West Nile virus (WNV) is a single-stranded RNA virus of the flaviviridae family. The primary hosts are birds, and humans can be infected through transmission by mosquitoes. WNV is enzootic in Africa, Europe and Asia, and is also endemic in the United States, where over three million infections have occurred between 1999 and 2010 [78]. In endemic regions, WNV accounts for a significant proportion of encephalitis cases [28, 79]. In the United States, WNV was the second leading cause of viral encephalitis in the 2000–2010 period [28]. WNV can also cause massive outbreaks worldwide [80]. In Europe, the incidence of WNV disease rose sevenfold in 2018 (from the previous year), with a total 181 deaths [81]. A severe outbreak was also experienced in Romania, where incidence peaked at 1.5/100,000 in the year of 1996.

Mechanisms of infection

Although the exact disease mechanism is unknown, current hypothesis suggests the WNV enters the CNS hematogenously after crossing the blood–brain barrier, by endothelial replication or through transneuronal axonal transport within olfactory or peripheral somatic nerves [82].

Clinical manifestations

Most cases are mild or asymptomatic. Nervous system involvement (meningitis, encephalitis, acute flaccid paralysis) occurs in 1% of patients. Acutely, WNV encephalitis (WNE) patients usually present with fever and encephalopathy. Movement disorders, including myoclonus and parkinsonism, and motor weakness are common [83]. Mortality rates can be as high as 15–20%, with older adults at a higher risk [84].

Impacts on cognition

WNE patients experience significant morbidity during the initial months following acute infection. Most cases require rehabilitation [85, 86]. Movement disorders persist for months to years [83, 87–91]. Eighty percent of WNE patients report persistent WNV-related symptoms one year after infection.

Using comprehensive neuropsychological assessment tools, [88] showed that patients with neuro-invasive WNV disease displayed mild cognitive deficits in immediate and delayed memory, and more significant cortical thinning than controls on magnetic resonance imaging [88]. These findings were supported by another study conducted in Canada [89].

Aseptic meningitis

Molecular biology and epidemiology

Although the exact cause is unknown in many cases, viral meningitis is a leading cause of aseptic meningitis (AM) worldwide. Viral meningitis accounts for roughly 40% of all AM cases [92, 93]. The rates of detection of causative pathogens, particularly viruses, increases as more molecular and immunological tests are used [94], and the diversity of AM-causing viruses is ever-increasing [95], so many physicians consider AM of unknown cause as presumably of viral etiology [96]. Enteroviruses, VZV and herpes simplex virus type 2 are common causative agents.

Mechanisms of infection

In aseptic meningitis, mechanisms of infection are specific to the underlying infection associated. Herpes simplex and VZV-associated aseptic meningitis are usually associated to reactivation and its associated mechanisms, as described above. Human enteroviruses, a major cause of AM worldwide, are primarily acquired through the fecal–oral or fecal–hand–oral route (and occasionally by aerosolized oral secretions). Following infection in the oropharynx, the virus spreads to the gastrointestinal tract. The following viremia is occasionally followed by entry to the central nervous

system through hematogenous spread [97, 98]. Once the virus enters the cerebrospinal fluid, it triggers accumulation of inflammatory cells, release of inflammatory cytokines, such as interleukin (IL)-1B, IL-6 and tumor necrosis factor (TNF)-alpha, which leads to increased permeability of the blood–brain barrier and additional inflammation, leading to typical symptoms of meningeal irritation [97].

Clinical manifestation

AM encompasses a clinical syndrome including patients with clinical and laboratory signs of meningitis, such as headache and nuchal rigidity, for which a bacterial cause of meningitis is excluded [26]. These symptoms of meningitis frequently follow prodromal systemic symptoms that are specific to the associated infection: shingles in VZV-disease, respiratory symptoms in enterovirus D68, diarrhea and hand-foot-and-mouth syndrome in other human enteroviruses [99]. The hallmark that differentiates AM from encephalitis is absence of altered mental status, which is the major diagnostic criterion for encephalitis, which is usually accompanied by absence of parenchymal abnormalities on neuroimaging and electroencephalogram studies [25].

Impacts on cognition

Acute AM is usually considered a benign condition not associated with long-term neurological sequelae. The perceived benign course may reflect, in fact, an underestimation of cognitive impairment in acute viral meningitis, due to the paucity of studies assessing quality of life and neuro-cognitive outcomes in this condition, as compared to the widely recognized consequences of acute bacterial meningitis (BM) and acute viral encephalitis (VE) [100].

Longitudinal studies in AM did not report a significant morbidity in the long term [24, 100, 101]. The inclusion of comprehensive tools for mental status and cognition revealed that AM patients might present with subtle visual memory and cognitive processing speed impairment [24], and worse global mental health status, compared to healthy controls. [101, 102].

Influenza viruses

Molecular biology and epidemiology

Influenza viruses are single-stranded RNA viruses of the Orthomyxoviridae family. Influenza types B and C infect predominantly humans and typically do not cause pandemics. Influenza type A viruses may infect other mammals and avians, which leads to mixing genetic material and epidemics in naïve populations. Influenza viruses, including the most common subtypes A (H1N1), A (H3N2), B (Victoria),

and B (Yamagata) are common causes of acute lower respiratory infections in humans [103], accounting for at least four large-scale pandemics in the last century [104]. An important complication of influenza infection (but not exclusive of it) is the acute respiratory distress syndrome (ARDS), which affects 200,000 patients yearly in the United States, accounting for more than 10% of total ICU admissions, with a hospital mortality risk of 30–40% [105].

Mechanisms of infection

Influenza virus is transmitted primarily by infection of epithelial cells within the respiratory tract following inhalation. The virus then spreads to the upper and lower respiratory tracts causing the flu or viral pneumonia. The pathogenesis of both ANE and encephalopathy associated with influenza are poorly understood. Although some researchers suggested a direct role for brain infection in encephalopathy, viral particles are seldom recovered from CSF or brain samples [106]. Alternatively, encephalopathy patients frequently show high levels of serum and CSF cytokines, suggesting cytokine-mediated inflammation/cytokine storm as a potential cause [107–109].

Clinical manifestation

Influenza causes uncomplicated flu in a majority of cases. Although influenza viruses were not consistently shown to cause infective encephalitis in humans or animal models, they occasionally cause encephalopathy, usually presenting with normal CSF profile [110]. Rarely, influenza infections lead to severe encephalopathy with coma, extensive abnormalities on neuroimaging and high mortality rates, a syndrome called acute necrotizing encephalopathy, which affects largely children but also adults [111].

Impacts on cognition

Experimental studies show that the injection of Influenza A virus in mice's olfactory bulb caused cognitive impairment 14–20 weeks after the infection [112] as well as hippocampal morphology changes [113]. A case of severe amnesia with hippocampal imaging abnormality following Influenza A infection has been reported [114]. Other studies showed that Amyloid- β protein has antimicrobial properties [115], specifically against Influenza A [116], which can explain its increased deposition in susceptible individuals (in special older adults) exposed to Influenza viruses. Additionally, influenza vaccination may decrease dementia risk in patients with chronic diseases [117, 118], underscoring a potential role of Influenza in human dementia.

Furthermore, cognitive impairment is very common in ARDS survivors. Seventy to 100% of ARDS patients are

cognitively impaired on hospital discharge, 46–80% one-year post-discharge, and 20% after five years [119, 120]. Moreover, one-year post-discharge, ARDS survivors show high rates of anxiety, depression, executive dysfunction and post-traumatic stress disorder [121, 122]. Persistent cognitive impairment was reported after a 2-year follow-up: roughly half of patients displayed signs of cognitive impairment [123]. Putative biological mechanisms underlying long-term cognitive impairment in ARDS patients include hypoxia, cytokine-mediated damage, cerebral autoregulation disruption, and blood–brain barrier damage-associated decrease in Amyloid- β clearance [124].

Coronaviruses and COVID-19

To our knowledge, no articles have investigated cognitive decline/impairment following the middle east respiratory syndrome (MERS) or the severe acute respiratory syndrome-coronavirus-1 (SARS-CoV-1). Although several studies have reported neuropsychiatric symptoms associated with the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) [13, 125], evidence of SARS-CoV-2 impact on human cognition remains scarce. Coronavirus disease 2019 (COVID-19) is caused by a RNA virus of the Coronaviridae family, and has been initially recognized as an agent of severe acute respiratory syndrome-related coronavirus (SARS-CoV) [126]. Although initially regarded as affecting the respiratory system with occasional gastrointestinal symptoms [127], subsequent reports showed that COVID-19 may also affect other major body organs, including renal, cardiovascular, and central nervous systems (CNS) [16, 125, 128].

COVID-19 has been recognized as a disease with pandemic consequences by World Health Organization in early March, 2020 [129]. Thenceforth, it has been infected almost 200 million people and killed more than 2.6 million people around 223 countries the world [130]. Especially in low- and middle-income countries, such as Brazil, due to the lack of vaccines, this number is still rising [130]. Furthermore, lack is known about the effect of the vaccine on new variants of SARS-CoV-2 [131].

Based on a review of the available literature, some authors predicted a high incidence of psychiatric morbidity following the COVID-19 pandemic, such as depression, anxiety and post-traumatic stress disorder [132]. Emotional symptoms can be related to COVID-19 through interaction with major life events and psycho-social stressors [133–135] or arise from disruption of brain function and damage to nervous tissues [17, 136]. Recent reports highlighting the risk for neuropsychiatric impairments secondary to COVID-19 showed that SARS-CoV-2 infection is associated with non-negligible incidence of neurological and psychiatric

manifestations and provided evidence that neuropsychiatric and cognitive symptoms may arise as a direct CNS infection by the virus also [17, 136].

Most studies on cognitive changes following SARS-CoV-2 infection focused on acute changes, mainly acute encephalopathy [137–139]. The occurrence of persistent cognitive deficits resulting from COVID-19 infection remains uncertain. Preliminary studies of convalescent COVID-19 patients using comprehensive neuropsychological assessment showed cognitive impairment two to four weeks after infection. Attentional deficits were the most relevant changes [140, 141]. A recent population-based study showed that 26% of all those with neuropsychiatric disorders due to COVID-19 had a dementia-like syndrome, with a median patient age of 71 years [136]. Another study showed that cognitive impairment (mainly attention and executive dysfunctions) has been reported in 28–56% of patients with mild or asymptomatic COVID-19, which was correlated with decreased cortical thickness in the right gyrus rectus, and in language associated areas [17]. A recent article showed changes in working memory, set-shifting, divided attention, and processing speed in a cohort of 57 patients recovering from moderate/severe patients with COVID-19, not being associated with intubation length, psychiatric and clinical diagnosis [142].

MRI studies have shown brain structural and microstructural changes in COVID-19 patients [143–146], such as acute necrotizing encephalopathy [145], cortical signal intensity abnormalities and unilateral FLAIR or diffusion hyper-intensities in medial the temporal lobe (MTL) [144, 146] and hippocampal abnormalities [143, 147]. A small case series of COVID-19 patients with acute encephalopathy suggested that the disease may be associated with a specific frontal hypo-metabolism pattern on FDG-PET [148] that differs from usual findings in delirium [149]. These abnormalities are associated with encephalitis and may at least partially explain cognitive impairment in COVID-19.

SARS-CoV-2 may cause neuropsychiatric symptoms by various indirect mechanisms, such as a hypercoagulable state, neuro-inflammation, immunological and epigenetic changes [132]. Several studies implied that blood–brain barrier disruption is associated with encephalopathy, favoring the neuro-inflammation theory [150, 151]. A possible mechanism for this theory might be hyper-activation of P2X7 receptors and a consequent NLRP3 inflammasome stimulation, triggering the inflammatory cascade [152]. The finding of coronavirus RNA in brain tissue of deceased patients raised the possibility of a direct brain injury mechanism [153]. This observation was corroborated by the finding of the virus in neural and endothelial cells in frontal lobe tissues [154], and in the cerebral spinal fluid of infected individuals [147, 155, 156]. Additionally, SARS-CoV-2 was found in astrocytes of all deceased patients with brain

damage, underscoring the fact that brain may be a sanctuary for SARS-CoV-2 [17]. A recent article found SARS-CoV-2 virus in 53% of brain tissues of people who died by COVID-19, even though brain lesions were non-specific and could not be attributed to SARS-CoV-2 lesions directly [157]. SARS-CoV-2 RNA, however, is rarely identified in CSF samples of COVID-19 patients [158], and most cases of COVID-associated neurological symptoms are CSF-RT-PCR-negative, including encephalopathic patients [128, 137, 159]. CSF analysis of patients with neurological symptoms showed SARS-CoV-2 immunoreactivity, resulting from serum antibody leakage to the CSF, rather than to intrathecal antibody production [150, 160].

Knowledge acquired from other CoVs outbreaks (SARS-CoV and MERS-CoV) has suggested potential neuro-invasive routes. The upper airways and the olfactory neuro-epithelium, are the initial step for odor identification [161, 162]. Olfactory cells express angiotensin-converting enzyme isoform 2 (ACE-2) and type II serine protease (TMPRSS-2), which may represent the viral entry point to the CNS [163]. Several RNA viruses can undergo axonal transport to different brain structures causing acute encephalitis [164–166]. A recent study pointed out to the neural–mucosa interface in olfactory mucosa as a potential port of CNS entry for SARS-CoV-2 [167]. Finally, the cytokine storm theory proposes that SARS-CoV-2 inflammatory response in the CNS is mediated by the massive glial cell cytokine release, such as IL1b, IL-6, and IFN I-III [168, 169]. Low ACE-2 expression is noted in both neurons and glial cells [170].

Intranasal SARS-CoV-1 inoculation (80% homology to SARS-CoV-2) in K18-hACE2 mutant mice (with the human form of ACE-2) resulted in the viral presence throughout the CNS, and was associated with local inflammatory mediators, respiratory dysfunction, and high mortality, with only mild lung infection [171, 172]. These findings suggest the importance of a CNS mechanism in virus-induced evolution and respiratory complications. CNS expression of ACE-2 expression in the CNS cells cannot isolatedly account for susceptibility to infection. Lungs and intestines usually show significant signs of viral infection and inflammation, which may be associated with high ACE-2 levels in pneumocytes and enterocytes. However, endothelial cells, which also express high ACE-2 levels do not display correspondingly high SARS-CoV infection levels [173].

In addition to the passage through the nasal neuro-epithelium route, independently from lower airway passage, evidence is accumulating suggesting that the virus initially infects peripheral nerve terminals and, through a trans-synaptic mechanism, enters the CNS [174]. Trans-synaptic routes have been reported in different coronaviruses (CoVs), such as HEV67 [175, 176] and in the avian bronchitis virus [177, 178]. Direct dorsal root ganglia infection in rats resulted in the presence of SARS-CoV in the CNS

[176]. Electron microscopy data confirmed the presence of the virus in neuronal vesicles. CNS viral invasion can occur through vagus nerve mediated trans-synaptic route, through intranasal inoculation of the influenza virus [177]. Partially (ipsilaterally) vagotomized animals inoculated with the virus showed viral presence in the root ganglia, bilaterally. The virus reached the ganglion contralateral to the de-afferentation first, suggesting a less effective transport after vagus nerve injury. In SARS-CoV-2, trans-nasal and trans-synaptic mechanisms might allow the virus to invade the olfactory bulb and brainstem, with both being the possible initial site for CNS invasion [179]. Once the virus enters the CNS, it affects neurons, microglia, oligodendrocytes, and especially astrocytes, undermining neurons viability [17, 179, 180].

Abate et al. [18] reviewed the different mechanisms by which SARS-CoV-2 infection might increase Alzheimer's disease (AD) risk, which could be extrapolated to other cognitive diseases. Direct viral neuro-invasion, as hypothesized above, and its association with ACE-2 expression in brain, especially in glial cells, could lead to oxidative stress and neuronal loss, due to both microglia and astrocyte activation, and increased nitric oxide (NO) production. [181, 182]. The finding that SARS-CoV-2 infects astrocytes [17] and its role with amyloid- β (A β) deposition, underscores a possible link between COVID-19 infection and AD. A β has also been shown to act as an antimicrobial peptide that may be overproduced in an immunologic mechanism [115]. Additionally, individuals with the ApoE3 allele may be more susceptible to severe forms of COVID-19 disease [183]. The connection between ApoE4 genotype, neuro-inflammation, and AD pathology should be further investigated [184]. Additionally, hypercoagulable states may induce

micro-vascular disease and induce vascular dementia and AD [185]. Figure 1 summarizes the neurobiological impact of SARS-CoV-2 on cognition.

Clinical implications

It is important that health professionals be aware of the potential impact of COVID-19 in Central Nervous System, especially in cognition. It could impact not only older individuals with cognitive impairment, but also healthy individuals more susceptible to it. More studies should be done to identify these susceptible individuals, its relationship with disease severity, the pathophysiological mechanisms of this impairment, as well as to understand the long-term consequences of the cognitive deficits. Health managers should also promote campaigns and continuing education programs to help physicians and other health professionals to identify and deal with these emerging issues.

Moreover, the need of an approach to deal with these cognitive impairments is urgent. The spread of cognitive rehabilitation techniques is indispensable, as it has been showed to be effective and can be used through several different cognitive deficits and etiologies [186]. Also, the use of therapeutic agents to prevent and treat cognitive impairment following virus infections has been recently proposed. Wozniak and Itzhaki [187] in a narrative review, pose the provocative question whether it is time to initiate using antiviral agents for AD. Previous research has found that the development of anti-herpes medications had a positive impact, reducing the incidence of AD [56]. Current randomized controlled trials (RCTs) are investigating the effect of antiviral therapy for

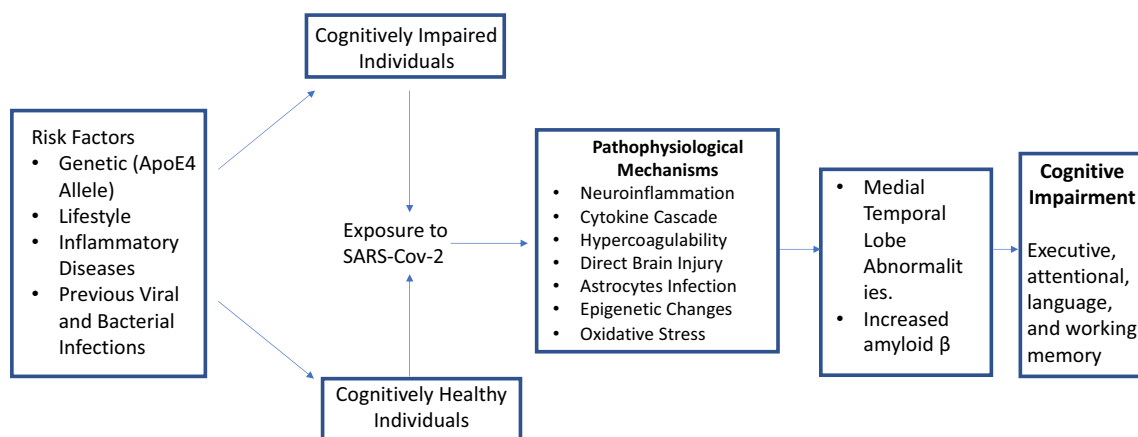


Fig. 1 Proposed pathophysiological mechanisms of the impact of SARS-CoV-2 infection on human cognition. First, risk factors, such as genetic, lifestyle, inflammatory diseases and previous viral and bacterial infections, might interact with exposure to SARS-CoV-2 in brains of both cognitively healthy and impaired individuals. It may induce several different mechanisms, such as neuro-inflammation,

cytokine cascade, hypercoagulability, direct brain injury, astrocytes infection, epigenetic changes and oxidative stress, which together may induce medial-temporal lobe abnormalities and/or increased amyloid- β . These different pathways might induce a cognitive impairment, mainly in executive, attentional, language and working memory areas

the treatment of AD [188]. Antibacterial therapy has also been suggested as an alternative for the treatment of senile dementia [10].

Some authors have suggested that due to anti-inflammatory properties, antimalarial drugs could be used to prevent neuropsychiatric COVID-19 complications [189]. Additionally, anticholinergic agent was proposed to reduce cytokine storm and A β deposition [190]. Furthermore, adamantane agents were suggested to play a potential neurocognitive protective effect in cognitively impaired patients [191]. So far, these agents were not proven to reduce mortality or morbidity due to SARS-CoV-2 infections.

Limitations

This paper has several limitations. First, due to the narrative nature of this review, there is a selection bias of articles. Second, we chose only six out of several different acute viral infections and virus-related syndromes. Our intent was to provide a wide scenario including both ubiquitous viruses causing disease worldwide (HSV-1, VZV, Influenzae), and viruses with marked regional relevance (WNV, JEV). Third, COVID-19 is an ongoing and dynamic epidemic. Many new articles are published daily, which makes reviewing this ever-changing field challenging. For instance, we made projections about post-COVID-19, because long-term studies on cognitive outcomes are largely lacking. We hope these projections will soon be confronted with original data from ongoing studies.

Conclusion

In sum, several viral agents have been shown to affect human cognition by distinct pathogenetic mechanisms. Some of these pathogens may cause long-term cognitive impairment, including parenchymal brain damage due to the direct CNS infection or to indirect mechanisms leading to disrupted brain function, such as hypercoagulable states and neuroinflammation. Recently, a wide body of evidence has shown that COVID-19 might lead to neuropsychiatric issues, especially cognitive impairments. However, lack is known about the pathophysiological mechanisms. Thus, it is crucial to understand the cognitive impact of acute viral infections and how it could be incorporate in the understanding of clinical impairments of COVID-19 in central nervous system. This knowledge may help us understand and predict possible long-term cognitive outcomes of COVID-19, helping both patients and health providers to cope better with this still unknown disease.

Declarations

Conflict of interest The authors declare no conflict of interest.

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