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The Two-Way Route between Delirium Disorder and Dementia: Insights from COVID-19

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Abstract
Background: Delirium disorder is a frequent neurological complication of SARS-CoV-2 infection and associated with increased disease severity and mortality. Cognitive impairment is a major risk factor for developing delirium disorder during COVID-19, which, in turn, increases the risk of subsequent neurological complications and cognitive decline. ***Summary:*** The bidirectional connection between delirium disorder and dementia likely resides at multiple levels, and its pathophysiological mechanisms during COVID-19 include endothelial damage, blood-brain barrier dysfunction, and local inflammation, with activation of microglia and astrocytes. Here, we describe the putative pathogenic pathways underlying delirium disorder during COVID-19 and highlight how they cross with the ones leading to neurodegenerative dementia. ***Key Messages:*** The analysis of the two-sided link can offer useful insights for confronting with long-term neurological consequences of COVID-19 and framing future prevention and early treatment strategies.

Introduction

COVID-19 pandemic has impacted our society, requiring urgent action and adaptation, catalyzing the scientific endeavor, and allowing the achievement of solutions at an unprecedented speed. Delirium, one of the most frequent neurological manifestations in

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COVID-19, is recognized as a risk factor and a forewarning of dementia [1]. Dementia burden is expected to massively grow in the next 30 years, with its prevalence estimated to triplicate in 2050 [2]. Actions to try and reduce the dementia burden include the urgency of increasing awareness, prevention, and adequate treatment of delirium [3].

The unusually high prevalence rate of delirium in COVID-19 patients and the scientific advances in the understanding of COVID-19 could thus offer a unique opportunity to gather insights about the link between delirium and dementia. We hypothesized that the pathogenic mechanisms involved in delirium disorder during COVID-19 are central in this link and could provide the terrain for the identification of future biomarkers. Here, we will analyze the connection between delirium disorder and dementia in both causal directions, first reviewing the literature in the pre-COVID-19 era and, later, highlighting how the putative pathogenic pathways involved in COVID-19 shed some light on the route between the two conditions.

Reconciliating the Concepts of Delirium and Acute Encephalopathy

Evolved through centuries, today "delirium" still refers to a clinical condition. Acute encephalopathy (AE) instead is an umbrella term to refer to a pathological process resulting from different possible combinations of multiple predisposing (or risk) factors, protective factors (which will determine the brain's ability to respond to damage), and precipitating (or etiological) factors. When such a process exceeds a certain threshold, clinical manifestations occur, ranging from subsyndromal delirium to coma (Fig. 1). Though allowing a prompt identification, the use of the term "delirium" or "acute encephalopathy" introduces some limitations. Indeed, progresses in the field would require the integration of neurobiological features and the combination of the clinical syndrome with an etiological or biomarker-based classification. Efforts in this direction have recently been made by suggesting an integration between the definitions of delirium and AE and recommending the use of specific terminology, such as delirium disorder (Box 1) [4, 5].

The Link between Delirium Disorder and Dementia: A General Overview

The interface between delirium disorder and dementia has been widely described. A diagnosis of cognitive impairment is widely reported as one of the main risk factors for developing delirium and sepsis-associated AE [6, 7]. Reversely, patients who suffered from delirium are at higher risk of developing a subsequent cognitive decline [8]. Although both disorders are multifactorial, they share common risk factors such as age, visual or hearing impairment, depressive disorder, physical inactivity, low social interaction, alcohol abuse, metabolic disorders, poor nutrition, or use of illicit drugs.

Acute encephalopathy and neurodegeneration seem to share pathogenic pathways at micro- and macro-scale levels. At a molecular and cellular level, an imbalance in neurotransmitters, loss of cholinesterase activity, the blood-brain barrier (BBB) dysfunction, and local inflammation with microglia and astrocyte activation are candidates as intersection points between the two conditions [9–11]. At a macroscale level, the hypothesis of a network disruption as a pathway leading to delirium is supported by the lack of gross structural abnormalities at brain imaging in more than half of cases [12]. Indeed, a reduced ability of network integration, mainly involving the frontal, limbic, and default mode network areas, could be a supposed predisposing factor for delirium disorder in older adults [13]. The same areas might undergo further structural and functional alterations during delirium disorder, which could trigger or accelerate cognitive decline [14].

Whether delirium occurrence is higher in patients with a specific underlying neurodegenerative process is still uncertain. So far, studies on delirium in older adults have struggled to identify a single predisposing neurodegenerative pattern, including ischemic load, neuritic amyloid plaque, neuronal loss in the substantia nigra, or α-synucleinopathy [15]. Nonetheless, delirium has been observed more frequently in patients with late-onset Alzheimer's disease (AD) and vascular dementia rather than in those with early-onset AD or fronto-temporal dementia [16]. Moreover, lower cerebrospinal fluid (CSF) beta-amyloid-42 ($A\beta_{42}$) or 40 ($A\beta_{40}$) over tau (Aβ/tau) levels and neuroimaging features, such as the presence of white matter hyperintensities, infarcts, and temporal atrophy, have been described in individuals at higher risk of developing delirium [17–19]. On the other side, the occurrence of delirium disorder seems to accelerate cognitive impairment irrespective of the neuropathological substrate. Indeed, patients with stroke or traumatic brain injury who developed delirium were at higher risk of subsequent dementia [20, 21], and the presence of delirium accelerated cognitive decline in patients with AD [22]. However, the memory domain emerges as the most affected by delirium [23], and, in animal models, the hippocampus resulted to be the most vulnerable region during induced sepsis [24]. Moreover, hippocampal lesions and increased atrophy in fronto-parieto-temporal cortices were observed after delirium [18, 25].

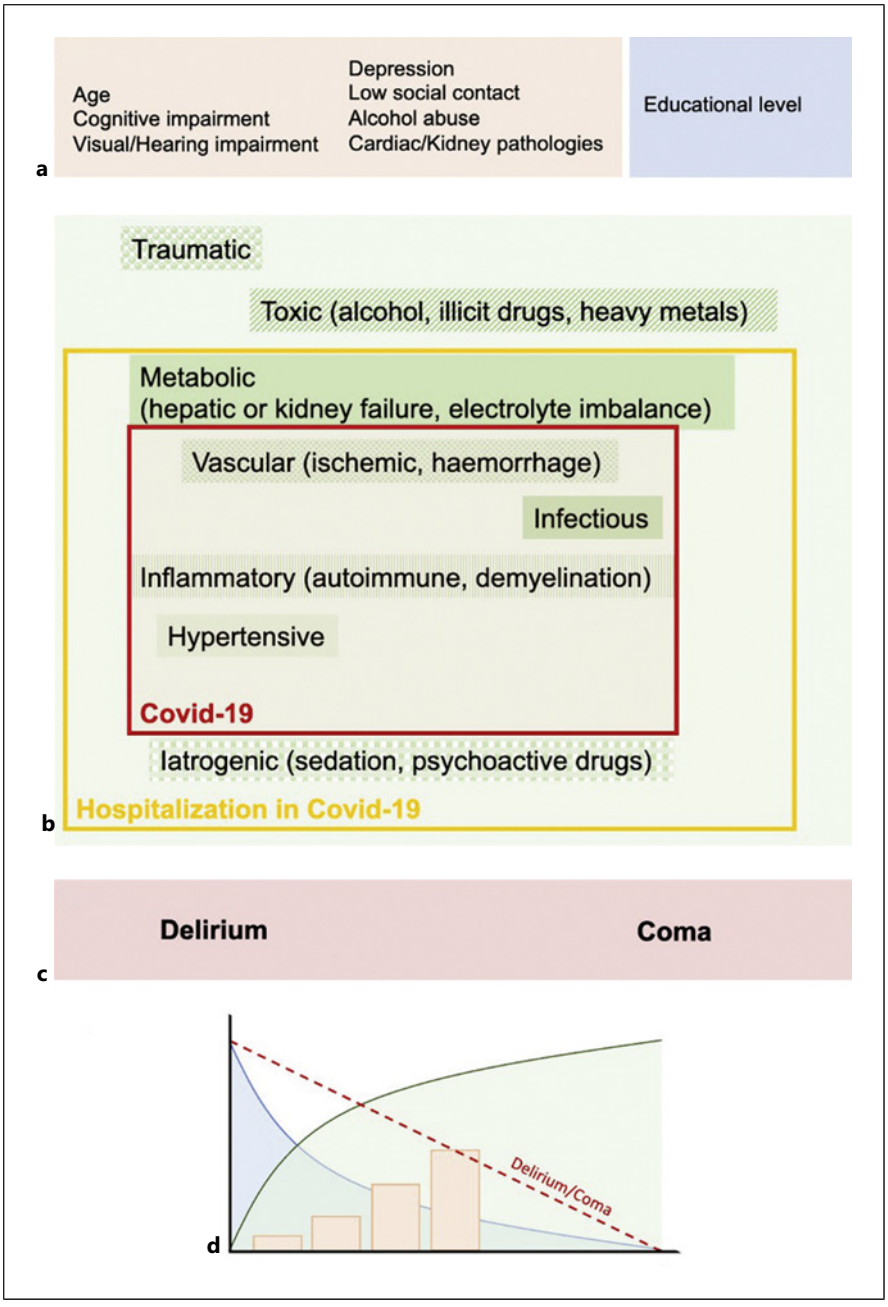

Fig. 1. AE and its clinical manifestations, interaction among protective, risk, and predisposing factors. **a** Risk and protective factors for AE. **b** Precipitating (or etiological) factors for AE; red box: factors involved in COVID-19; yellow box: factors involved in hospitalized COVID-19 patients. **c** Clinical manifestations of AE. **d** The threshold for clinical manifestations during AE (dashed red line) is likely to decrease as patients would present with an increasing number of risk factors (in orange), a more severe precipitating factor (in green), and a lower brain's ability to respond to injury (in blue).

Delirium Disorder in COVID-19

Early during the pandemic, delirium has been described among the most frequent neurological manifestations of the acute phase of COVID-19, affecting up to the 65% of patients [1], and it has been associated with an increased duration of hospitalization and higher mortality [26]. A baffling and noteworthy aspect was its manifestation as a very early or symptom onset [1, 27], especially in older adults or individuals with cognitive impairment [26]. The latter fits within the emerging evidence of a relationship between COVID-19 and cognitive impairment, strong and not unidirectional. Indeed, patients with dementia are at a greater risk of developing COVID-19 [28] and present with increased disease severity and risk of mortality [29]. Moreover, patients with a frail condition such as dementia have also been among the ones who most suffered from the contingent restriction measures

Box 1. AE and delirium: clarifying the nomenclature

Delirium is defined according to the DSM-5 as a *disturbance in attention and awareness, which develops over a short period of time, represents an acute change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day* and *with evidence that the disturbance is a direct physiological consequence of a medical process, substance intoxication or withdrawal, exposure to toxins, or multiple etiologies* [109]. Acute encephalopathy can be defined as *a rapidly developing (over less than 4 weeks, but usually within hours to a few days) pathobiological process in the brain* that clinically manifests as subsyndromal delirium, delirium, or altered status of consciousness [4]. As recently pointed out, the terms acute encephalopathy and delirium have been frequently used in an alternate way in literature, though the definition of delirium refers to a clinical state and acute encephalopathy to the underlying pathophysiological process [4]. Therefore, while delirium diagnosis is based on the acute onset of altered attention and awareness, occasionally associated with other cognitive deficits and secondary to any unspecified medical condition, the definition of acute encephalopathy includes the etiology and the possible pathophysiological mechanisms causing delirium or impaired consciousness. Here, we will preferably refer to delirium disorder and to a COVID-19-related delirium disorder, in an effort of integration, as suggested by [5]. We will mainly focus on the pathological substrates linking it to dementia while discussing delirium as the frequently reported clinical manifestation of acute encephalopathy and representative of the final pathway of pathogenic mechanisms in COVID-19. Nonetheless, the terms "delirium" and "acute encephalopathy" could still be used when referring to existing studies or when referring specifically to clinical manifestation or pathogenesis, respectively.

[30]. On the flip side, studies are revealing the short- and medium-term effects on cognition that this pandemic could bring [31, 32], with a striking rate of association between delirium and neurological complications after 6 months [33].

Regarding the underlying physiopathology, neuroimaging features ranging from hypometabolism in fronto-insular and subcortical regions, acute ischemic lesions, leukoencephalopathy, hemorrhages, and microbleeds [34, 35] have been reported in COVID-19 patients with AE. The heterogeneity of the imaging patterns probably reflects a combination of multiple factors. Precipitating factors likely to contribute include ICU procedures, hypoxia, superimposed sepsis, electrolyte imbalance, and multiorgan failure. Notably, delirium in patients with COVID-19 who required ICU admission was more severe but not more frequent when compared to non-COVID-19 ICU patients [36]. Among risk factors, a low social interaction due to restriction measures adopted during the pandemic is to be included, as family visiting correlated to lower delirium occurrence in the intensive care unit (ICU) [37]. Albeit risk and precipitating factors can be miscellaneous, pathogenic mechanisms specifically related to SARS-CoV-2 infection, such as (i) the endothelial damage and coagulopathy, (ii) the dysregulation of the host immune system, (iii) the direct viral injury, (iv) the renin-angiotensin-aldosterone system (RAAS) imbalance, likely contribute to the development of AE in patients with COVID-19:

Endothelial Damage and Coagulopathy

Pathological and imaging features of brain endotheliopathy in COVID-19 have been widely described, mirroring the more spread systemic involvement of the endothelium [38]. In the brain, vascular elements, such as endothelial and pericytes of intraparenchymal vessels, express angiotensin-converting enzyme 2 receptor (ACE2-R) [39, 40]. A direct infection of brain endothelial cells has been detected in primates infected with SARS-CoV-2 [41]. Besides, endothelial activation and BBB dysfunction can be induced by the SARS-CoV-2 spike protein [42]. Other possible contributors to BBB and brain endothelial damage are hypoxia and inflammatory response. Regardless of the triggering mechanism, the brain endothelium damage and BBB dysfunction could lead to the local release of prothrombotic molecules and pro-inflammatory cytokines, along with increased oxidative stress and impaired regional vascular perfusion, contributing to AE occurrence. In pre-COVID-19 studies, markers of endothelial and BBB dysfunction (PAI-1, S100B, and E-selectin) have been related to delirium occurrence and duration [43], corroborating the hypothesis of a major role of endotheliopathy in AE during COVID-19.

Patients with COVID-19 showed higher plasma concentrations of D-dimer, fibrinogen, and factor VIII, indices of hypercoagulability. The increased levels of von Willebrand factor, soluble P-selectin, thrombomodulin, and plasminogen activator inhibitor-1 (PAI-1), together with a preserved antithrombin, protein C, and protein S activity, suggest that the hypercoagulability observed in COVID-19 is possibly mediated by the endotheliopathy [44, 45] and, at the brain level, promoted by altered cerebral blood flow autoregulation [39]. Besides, although described in other conditions characterized by lung injury and thus not specific to COVID-19, the presence of

entrapped megakaryocyte in brain capillaries could have a role in AE [46, 47].

Inflammation

A dysregulation of the host immune response emerged as a crucial player in determining COVID-19 severity and outcome. IL-1, IL-6, IL-8, IL-10, and TNF-α levels are increased and, together with the modulation of different types of IFN and T lymphocyte response, have been associated with disease severity and mortality [48]. Inflammation has also been regarded among the main mechanisms responsible for neurological symptoms in COVID-19, at least in the acute phase. This hypothesis is supported by the positive response of COVID-19 patients with AE to steroid, immunoglobulin, or immunomodulatory treatments [49, 50]. Higher levels of cytokines in the serum and CSF were detected in patients with AE during COVID-19 [51]. Moreover, even in patients with mild respiratory symptoms, Fernandez-Castaneda and coauthors found increased levels of cytokine associated to microglia activation and impaired hippocampal neurogenesis in mice [52].

Vascular Autonomic Imbalance

An altered balance in RAAS, involving the *ACE2-Angiotensin (1-7)-Mas Receptor* and *ACE-Angiotensin II-Angiotensin II Type 1 Receptor (AT1R)* pathways, could also contribute to delirium disorder in COVID-19. Following SARS-CoV-2 infection, there is a decrease in ACE2-R function and a downregulation of its expression, resulting in an increase of circulating levels of angiotensin II (Ang II) [53]. Increased Ang II levels induce the release of reactive oxygen species (ROS), vasoconstriction, increased sympathetic outflow, water intake, and stimulation of fibrosis and inflammation. In animal models, a capillary vasoconstriction, mediated by reduced levels of Ang (1-7) and increased levels of Ang II, and the action of Ang II on the AT1-R expressed on pericytes, has been observed after mimicking the viral binding of ACE2-R receptors [39]. During COVID-19, vascular autonomic balance can also be affected by cardiopulmonary and renal damage or by the viral invasion of structures involved in autonomic regulation, as the solitary tract nucleus. An autonomic dysfunction with an abnormal sympathetic response has been showed in older adults with delirium [54], suggesting its contribution in AE.

Direct Viral Damage

A direct invasion of the brain from SARS-CoV-2 and its clinical consequences are still debated. Proposed routes of the virus entry include a hematological route – through the cells at the blood-brain interface, an olfactory, and a trans-axonal/trans-synaptic route – through peripheral nerves. Brain damage could also be caused by the viral spike protein as it has been showed to cross the BBB and induce endothelial damage in animal models [55]. The hematological route implies an entry through components of the BBB, such as the endothelial cells, where ACE2-R is expressed. Another theory involves the entry through the blood-CSF barrier as ACE2-R is expressed in choroid plexus epithelial cells. Indeed, their direct infection by SARS-CoV-2 has been demonstrated, with subsequent dysfunction of the blood-CSF barrier [56]. In the past, the olfactory nerve has been suggested as an entry route for other viruses, such as influenza virus, through the olfactory receptors and then anterogradely to the olfactory bulb or across the olfactory ensheathing cells [57]. ACE2-R has been found on the olfactory mucosa, where the SARS-CoV-2 has been detected, but it is not expressed in the olfactory bulb [58]. Therefore, although anosmia is likely related to the viral replication in the olfactory neurepithelium, a brain invasion through the olfactory nervous tract is still debated [59]. Lastly, a retrograde entry through other cranial nerves, such as the vagus or the carotid sinus nerve, has been considered. This hypothesis is supported by the virus detection in the brainstem, the presence of ACE2-R in the nucleus tractus solitarius and dorsal motor nucleus of the vagus [60], and the putative link with the autonomic symptoms observed in COVID-19. Overall, anatomopathological studies have inconsistently found viral RNA or protein in the brain, and the presence of SARS-CoV-2 RNA in the brain did not correlate to other features of tissue damage [40, 61, 62], suggesting a limited role for a direct neural invasion in causing neurological symptoms. However, using in vitro and in vivo models, the potential invasion of neurons by SARS-CoV-2 has been demonstrated and related to neuronal death and metabolic alterations [63].

Hypothesis: A Two-Way Route between Delirium Disorder and Dementia in COVID-19

The pathogenic pathways responsible for delirium disorder in COVID-19 patients can be fostered by an underlying neurodegenerative process, which would explain the high rate of delirium observed in older adults and patients with cognitive decline. In turn, we suggest that the same pathways can trigger or accelerate neurodegeneration, thus mediating the onset or progression of cognitive impairment (Fig. 2).

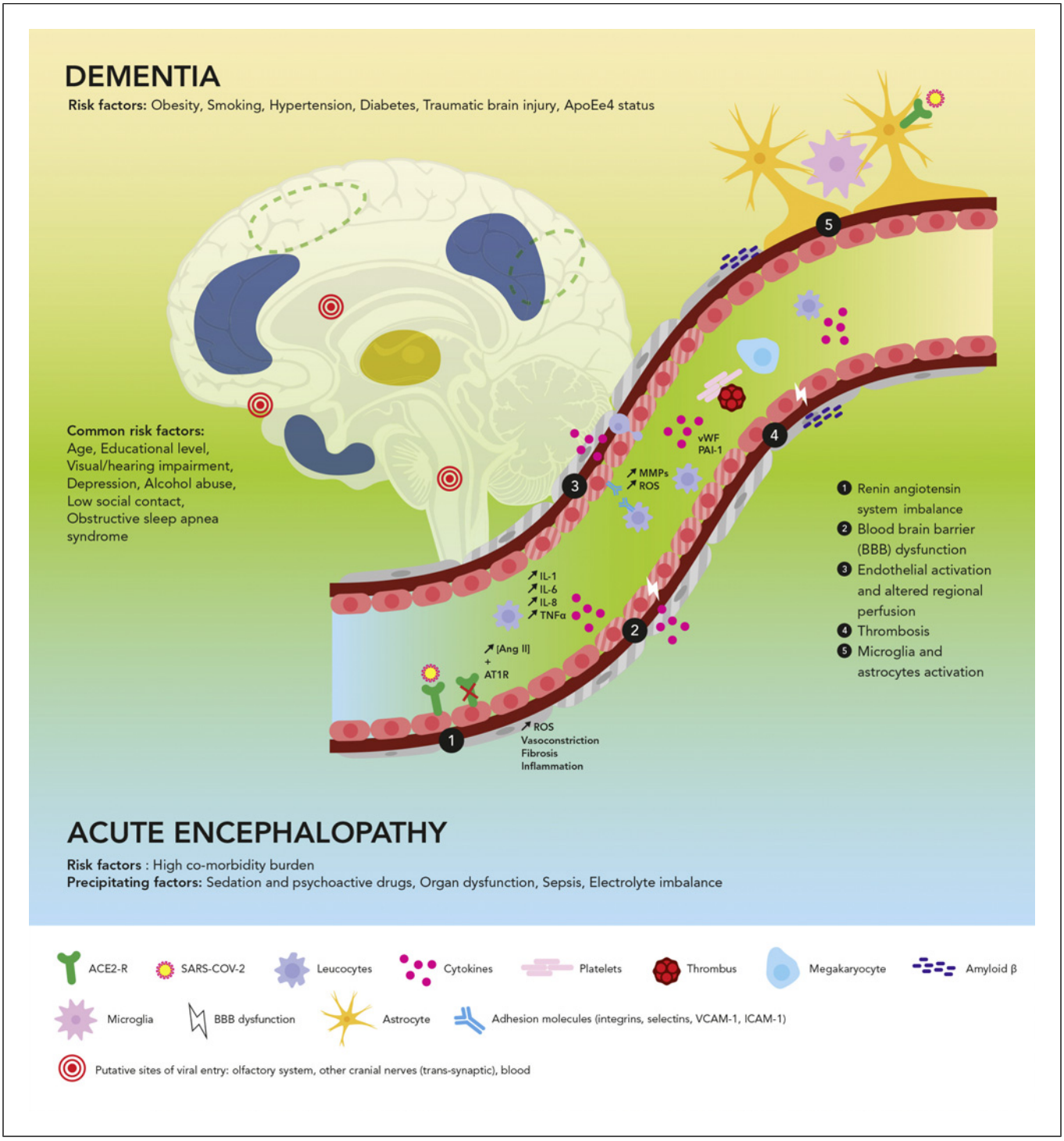

Fig. 2. Pathogenic mechanisms at the interface between AE in COVID-19 and neurodegeneration in dementia. The binding of the virus to ACE2-R receptors results in a decrease in function and a downregulation of ACE2-R expression, with subsequent imbalance of the ACE2-R-Ang (1-7)-Mas and ACE-Ang II-AT1R pathways. The release of Ang II causes increased levels of ROS, with subsequent endothelial and pericyte damage, local vasoconstriction, and fibrosis and promotes inflammation. Moreover, cytokine release, possibly amplified by endothelial damage, induces the upregulation of oxidative stress pathways, vasoconstriction, BBB dysfunction, and platelet activation. Platelet activation, endothelial release of vWF, and the recruitment of megakaryocytes result in thrombotic events. Inflammation is favored by local BBB breakdown and amyloid beta (Aβ) deposits, resulting in microglia and astrocyte activation, which can also be damaged by direct viral binding. On the left are the highlighted brain areas likely involved: default mode network and temporal regions (blue), attentional networks (dashed green), and subcortical structures (yellow).

This cycle would have its main setting at the level of the neurovascular unit, and it could lead to local ischemia and boost abnormal protein deposition. The entry into this cycle could take place only over a certain threshold or in the presence of a combination of more mechanisms. At a large-scale level, specific brain regions or networks, including subcortical nuclei, the hippocampus, the default mode, and attentional networks, would be more vulnerable to this microvascular damage. Mechanisms specific to SARS-CoV-2 infection, as well as its actions on endothelium, pericytes, and microglia, could explain the higher incidence of cognitive impairment in patients with COVID-19-related AE.

Underlying Neurodegenerative Processes Are an Optimal Milieu for AE in COVID-19

Endothelial Damage and Coagulopathy

Evidence of an ongoing endothelial dysfunction has been reported in both AD and cerebrovascular disease, potentially underpinning a further damage occurring during SARS-CoV-2 infection. In patients with AD, altered endothelial mitochondrial pathways, a loss of endothelial tight junctions, and a BBB breakdown have been described [64, 65]. Similarly, stroke and cerebral small vessel disease are associated with a sustained BBB breakdown [66]. Besides, risk factors for cognitive impairment, such as obesity, diabetes, hypertension, and obstructive sleep apnea disorder, are related to an increased severity of COVID-19 [67, 68]. Such metabolic disturbances induce endothelial dysfunction [69] and could therefore lower the threshold for brain injury caused by the pathophysiological changes occurring during COVID-19.

ApoE is also to be considered a possible contributor to AE in COVID-19 patients with an underlying neurodegenerative process. An in vitro study showed that ApoEε4 neurons and astrocytes were more likely to be infected by SARS-CoV-2 and were more susceptible to damage, compared to ApoEε3 cells [70]. Moreover, the ApoEε4 genotype has been associated with an increased risk of COVID-19 and higher disease severity, independent of comorbidities such as dementia, diabetes, and hypertension [71]. Recently, the same group found an association between ApoEε4 and the occurrence of delirium in COVID-19 [72]. Therefore, it can be hypothesized that, in COVID-19, ApoEε4 increases the risk of AE, which would contribute to the increased risk of aspiration pneumonia, distress, and short-term mortality [6].

A high rate of brain microhemorrhages has been observed in patients with COVID-19. Microbleeds had a heterogeneous distribution, being described at a juxtacortical, subcortical, corpus callosum, brainstem, and deep gray matter level [73–75]. Several hypotheses have been advanced to explain the high number of microbleeds in COVID-19, including hypoxia, coagulopathy, thrombosis, and endothelial damage. In particular, the juxtacortical and callosal localization suggested a hypoxia-driven mechanism as observed in critical-illness condition [76], while the lobar microbleeds, in some patients, could be linked to an amyloid-related vulnerability of the endothelium [77]. Indeed, cerebral amyloid angiopathy and markers of neurodegenerative conditions have been frequently found in patients with a fatal outcome [62]. Thus, it is tempting speculating that, in some patients, the high rate of microbleed detection could be a marker of a preexistent endothelial susceptibility to damage, possibly induced by Aβ perivascular deposition. However, this hypothesis deserves further investigations.

Inflammation

Previous studies revealed that an underlying neurodegeneration predisposes to damage induced by a systemic inflammation response, such as the one occurring in COVID-19. Transforming growth factor beta (TGF-β), a cytokine elevated in COVID-19, is not able to cross an intact BBB, while aging and BBB disruption result in an increased TGF-β-mediated signaling in astrocytes and subsequent neuronal damage [78, 79]. As above mentioned, IL-1, a cytokine released in the acute phase of COVID-19, triggers the cognitive dysfunction during acute inflammation in a mouse model of neurodegenerative disorder [9].

Autonomic Imbalance

An increased vulnerability to autonomic dysregulation is observed in patients with cognitive decline, and orthostatic hypotension has been reported in patients with Parkinson's disease, Lewy body dementia, AD, and vascular dementia [80]. Neurofibrillary tangles and Aβ plaques have been disclosed in the brainstem autonomic nuclei in patients with AD, including the nucleus tractus solitarius and the dorsal motor nucleus of the vagus [81]. Autonomic dysregulation is also frequent in metabolic syndrome and diabetes. Thus, it is plausible that aging and metabolic or neurodegenerative disorders offer a substrate for further autonomic dysfunction caused by direct viral damage or inflammation in the central autonomic nuclei [61, 62] or by a RAAS imbalance at a central or peripheral level, thus contributing to AE severity.

Direct Viral Damage

As discussed above, so far, there is discordant evidence of a direct participation of SARS-CoV-2 in triggering AE. However, in a modeling study, Kaneko and colleagues found that ACE2-R expression by the brain endothelium progressively increased with vessel size and flow rates. Authors suggested that local stenosis, and thus antecedent arteriopathy, can influence the regulation of endothelial ACE2-R expression and the subsequent binding of SARS-CoV-2 [82]. Therefore, it might be hypothesized that a preexistent arteriopathy could facilitate the viral binding to endothelium in the brain.

AE Triggers or Accelerates Neurodegeneration in COVID-19

Endothelial Damage and Coagulopathy

In COVID-19, endothelium was showed to express markers of inflammation, adhesion molecules such as VCAM-1 and ICAM-1, and cytokines, which are indicators of endothelial activation and dysfunction [69] and implicated in the pathogenesis of small vessel disease and vascular dementia [83]. Increased levels of CXCL8 and VEGF-A, produced by astrocytes and endothelial cells, were detected in the CSF of COVID-19 patients with AE, and the neurovascular unit was proposed as the central stage in its pathogenesis [51]. This has been confirmed in a recent autopsy study on patients with a broad range of clinical severity: endothelial activation, coupled with platelet aggregation, vascular leakage, and local inflammation were observed, resulting in microglia activation with neuronal injury and neuronophagia, prominently in the hindbrain [84]. A dysfunction at the level of the neurovascular unit has been suggested to trigger the pathogenic pathway leading to cognitive dysfunction in AD, as the damage to pericyte, induced by Aβ, and the release of ROS by perivascular macrophages under the effect of Ang II would result in neurodegeneration [85, 86]. A dysfunction of the perivascular unit components is also implicated in the development of dementia after traumatic brain injury, pinpointing the balance between endothelium, pericyte, microglia, and astrocyte as strategic in the process of neurodegeneration.

As mentioned above, the breakdown of the BBB observed in COVID-19 patients is caused by structural or functional endothelial damage [42, 56]. In patients with critical illness, markers of BBB disruption, such as S100B, were related with an increased long-term cognitive decline. A BBB leakage at the hippocampus level has been associated with aging and cognitive dysfunction [64] and, in patients with small vessel disease, it has predicted cognitive decline after 1 year of follow-up [66]. Lastly, the endothelial damage in the context of a systemic coagulopathy that characterizes the acute phase of COVID-19 generates thrombotic and hemorrhagic events that can increase brain vulnerability to neurodegeneration [39].

Inflammation

In human and animal models of COVID-19, brain levels of IL-1β and IL-6 were elevated, especially in the hippocampus and medulla oblongata [87]. Elevated CCL11 CSF levels and hippocampal microglial activation were found in pathological studies [61, 62] and animal models [52]. Subpopulations of astrocytes and microglia similar to the ones found in neurodegenerative disorders have been disclosed in the brains of patients with COVID-19 [88]. Finally, alteration of the lung microbioma from COVID-19 could affect the brain microglia, favoring its activation [89].

Both microglia and astrocyte activation have been related to the development of neurodegenerative disorders. Microglia dysregulation, together with astrocyte activation, induces tau hyperphosphorylation and Aβ oligomerization and could initiate or accelerate neurodegeneration. Indeed, microglia is involved in the clearance process of Aβ and tau, accomplishing a beneficial task until a non-turning point where a vicious loop sets up. This loop consists of an over-threshold inflammation process, through astrocytes activation, reduced microglia clearance ability, increased Aβ aggregation, seeding, and propagation [90]. Besides, recent findings point toward a parallel spatial propagation of microglia activation and tau deposition [91]. Lastly, increased microglia activation, particularly in the hippocampus, putamen, and cerebellum, has been linked to systemic inflammation [92].

Autonomic Imbalance

Besides the role of RAAS imbalance in ROS production, there is evidence of a polyhedric contribution to AD, including its role in increasing beta-secretase activity and Aβ levels, tau phosphorylation, and in reducing local blood flow [93].

Direct Viral Damage

Previous coronaviruses showed a potential for invasion and damage of the CNS. However, so far, no evidence suggests that SARS-CoV-2 can be directly implicated in a neurodegenerative cascade. Although longitudinal data are missing, when detected in the brain samples, the viral load was not associated with pathological damage or to leukocyte infiltration [41, 61–63]. Nonetheless, the entry into the CNS could be

facilitated by BBB and endothelial damage, as occurring during encephalopathy. Moreover, vascular and hypoxic damage have been recently observed close to sites of virus replication in brain organoids, possibly making these regions more vulnerable to ischemic damage [63]. Besides, infection of astrocytes by SARS-CoV-2 has been demonstrated in vitro, with subsequent activation and metabolic cellular distress [94]. Finally, SARS-CoV-2 proteins seem to have an amyloidogenic potential and are toxic for neural cells [95]. These data call for future longitudinal studies to verify whether a neurodegenerative process could be directly triggered by SARS-CoV-2 neuronal or glial cell invasion.

Delirium Disorder in COVID-19 and Dementia at a Brain Network Level

Although advanced neuroimaging data on COVID-19 are still few, the available studies indicate a predominant involvement of the medial/lateral frontal regions and of limbic structures during acute neurological dysfunction in patients with COVID-19, overlapping with attentional and default mode networks involved in neurodegenerative dementia. Specifically, ^{18}F-FDG-PET data revealed hypometabolism at the level of the prefrontal, insular, and middle temporal regions, with some of these abnormalities persisting at 6-month follow-up [35]. While functional MRI studies in the acute phase are still lacking, an intact default mode network functional connectivity has been suggested as a positive prognostic marker in patients with COVID-19 and AE [96]. Volumetric analyses found a reduced orbito-frontal and parahippocampal cortical thickness at about 4 months after SARS-CoV-2 infection [97]. Diffusion tensor imaging data are available in the acute/subacute phase of COVID-19 but with small sizes or heterogeneous samples. A study on 6 COVID-19 patients with encephalopathy disclosed diffused altered microstructure at the level of gray matter and the damage of several white matter tracts, including thalamo-cortical tracts [98]. Patients with subacute COVID-19 and a range of neurological symptoms showed white matter altered microstructure in the fronto-parietal areas, but also in basal ganglia and midbrain regions, and authors suggested a link with perivascular space distribution [99], referring back to vascular dementia. Future studies will assess whether the brain regions mainly affected during COVID-19 AE overlap with more susceptible dementia-related networks, whether they endure a further damage over the long term and whether they associate with cognitive decline.

Major Challenges

The Need of Disentangling

A major issue when assessing the relationship between delirium disorder in COVID-19 and dementia is the difficulty in disentangling the role of social isolation or infection control procedures. Patients affected by dementia showed a significantly greater loss in performance during the pandemic period [100], with the potential mediation of mental health deterioration [101]. Such factors represent a nontrivial addendum to the process of reaching the delirium threshold (Fig. 1) and will need to be tackled, distinguishing them to mechanisms specifically related to SARS-CoV-2 infection.

The Need for Biomarkers: Insights from COVID-19

In the pre-COVID-19 era, inflammatory markers, such as IL-6, hormones, growth factors, and neurotransmitters, were proposed as potential biomarkers, but without striking evidence for clinical use [102]. AD biomarkers, CSF Aβ and phosphorylated tau, were predictive of delirium, and NfL was recently found as a potential predictive and diagnostic biomarker [103]. These results have been confirmed in COVID-19 patients with AE, who presented with higher tau, glial fibrillary acidic protein, and NfL serum levels at admission [104]. Such validations in large samples acquire more importance in a context of the expanding role for serum biomarkers.

Genetic studies revealed that COVID-19 patients with ApoEε4 were at higher risk of severe illness and delirium [71, 72]. Other genetic crossroads have been found between AD and COVID-19 severity [105], and though not specifically investigated as predictors for encephalopathy yet, they could offer future roads to cover.

Regarding imaging and electrophysiological biomarkers, COVID-19 patients with AE were found to present with EEG abnormalities and frontal slowing [106], white matter hyperintensities, microbleeds, vessel wall enhancement, and frontal, insular, and temporal hypometabolism [41, 42]. These findings confirm and extend the role of altered white matter microstructure and the functional involvement of fronto-parietal regions in the pathogenesis of delirium.

Lastly, as pathological biomarkers, evidence emerged, during COVID-19 pandemic, of microglia activation at the level of the brainstem and hippocampus. This inscribes in a context where neuroinflammation is regarded as a significant pathogenic mechanism in dementia [91], and a clinical trial assessing the effects of a drug targeting the triggering receptor expressed on myeloid cells-2 (TREM2) in patients with early AD is ongoing. Further studies would determine the role of microglia activation in the link between AE and neurodegeneration.

Prevention and Therapeutic Implications

Vaccination policies drastically changed COVID-19 incidence and severity. However, older adults remain at risk of developing a severe infection [107]. While recent data suggest that delirium disorder is not more frequent in ICU patients with COVID-19 when compared to other diseases [36], data are still missing on its incidence among the vaccinated population, and reports suggest that up to 10% of older adults in nursing home, with neurocognitive disorders, can present with delirium after vaccination [108]. Thus, prevention through vaccination might not be sufficient, and adequate early recognition strategies and reduction of precipitating factors are needed in older adults with COVID-19. Moreover, although treatments such as high-dose steroids or immunoglobulins have been used to treat AE in COVID-19 [49, 50], systematic studies on the effects of anti-inflammatory or immunomodulatory drugs on delirium are lacking. Lastly, as brain endothelium and pericytes are central players during SARS-CoV-2 infection, the potential therapeutic or prevention effect of angiotensin receptor blockers on delirium disorder could be a further field for future investigations.

Conclusion

The risk of cognitive impairment as a long-term consequence of the COVID-19 pandemic has been advanced in the scientific community. Data emerged on neurological consequences several months after COVID-19, including increased incidence of cognitive decline. Given the reach of COVID-19 pandemic, the impact of an eventual cognitive decline triggered by SARS-CoV-2 infection could represent a tough challenge. The bidirectional link between dementia and AE in COVID-19 can offer a useful reading key to plan future research studies and early intervention. Lastly, as we witnessed in the last years, shedding light into COVID-19 pathogenesis can translate into a better understanding of non-COVID-19-related relation between AE and neurodegeneration.

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Conflict of Interest Statement

G.B., F.A., P.H.L., and G.A. have nothing to disclose. V.G. was supported by the Swiss National Science Foundation (projects 320030_169876, 320030_185028, and IZSEZ0_188355), the Velux Foundation (project 1123), and the Aetas and Schmidheiny foundations. G.B.F. reports receiving grants from the EC, IMI, the Swiss National Science Foundation, private donors, foundations, consultancy fees, and honoraria from a number of pharma companies in the field of drug development for Alzheimer's disease.

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Author Contributions

G.B. contributed to the conceptualization and manuscript drafting and reviewing; V.G. contributed to conceptualization and manuscript writing and editing; G.B.F. contributed to define the methodology and to manuscript drafting; F.A. supervised manuscript drafting and contributed to manuscript editing; P.H.L. contributed to validation of presented data and manuscript reviewing; and G.A. contributed to conceptualization, interpretation, and manuscript reviewing.

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