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SHORT COMMUNICATION

Acute-onset delirium in intensive care COVID patients: association of imperfect brain repair with foodborne micro-pollutants

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Abstract

Background and purpose: COVID-19 affects the brain in various ways, amongst which delirium is worrying. An assessment was made of whether a specific, long-lasting, COVID-19-related brain injury develops in acute respiratory distress syndrome patients after life-saving re-oxygenation.

Methods: Ten COVID+ patients (COVID+) with unusual delirium associated with neuroimaging suggestive of diffuse brain injury and seven controls with non-COVID encephalopathy were studied. The assessment took place when the intractable delirium started at weaning off ventilation support. Brain magnetic resonance imaging (MRI) was performed followed by standard cerebrospinal fluid (CSF) analyses and assessment of CSF erythropoietin concentrations (as a marker for the assessment of tissue repair), and of non-targeted CSF metabolomics using liquid chromatography high resolution mass spectrometry.

Results: Patients were similar as regards severity scores, but COVID+ were hospitalized longer (25 [11.75; 25] vs. 9 [4.5; 12.5] days, p = 0.03). On admission, but not at MRI and lumbar puncture performance, COVID+ were more hypoxic (p = 0.002). On MRI, there were leptomeningeal enhancement and diffuse white matter haemorrhages only in COVID+. In the latter, CSF erythropoietin concentration was lower (1.73 [1.6; 2.06] vs. 3.04 [2.9; 3.91] mIU/ml, p = 0.01), and CSF metabolomics indicated (a) increased compounds such as foodborne molecules (sesquiterpenes), molecules from industrialized beverages and micro-pollutants (diethanolamine); and (b) decreased molecules such as incomplete breakdown products of protein catabolism and foodborne molecules (glabridin). At 3-month discharge, fatigue, anxiety and depression as well as MRI lesions persisted in COVID+.

Conclusions: Some COVID+ are at risk of a specific delirium. Imperfect brain repair after re-oxygenation and lifestyle factors might influence long-lasting brain injuries in a context of foodborne micro-pollutants.

KEYWORDS
brain, COVID, delirium, erythropoietin, hypoxia, metabolomics

INTRODUCTION

Intensive care unit (ICU) patients often display acute fluctuation in their mental state together with inattention, disorganized thinking and an altered level of consciousness. In this setting suggestive of acute delirium [1] patients are likely to be subject to further complications and a worse outcome. Patients admitted for ventilation support of acute respiratory distress syndrome (ARDS) subsequent to coronavirus disease 2019 (COVID) are also at risk of developing neurological manifestations [2] that are worrying for three reasons: (a) a full understanding of their pathophysiology is lacking; (b) no aetiological treatment is available; (c) the long-term outcome of brain injury is uncertain. Clinical neurological presentations range from less severe conditions to serious damage depending on how the central nervous system (CNS) is affected. Although focal signs may be caused by cell necrosis attributable to the virus (reference [SR1]), there is a rising toll of COVID+ patients (COVID+) with neurological manifestations where magnetic resonance imaging (MRI) has detected multifocal abnormalities suggestive of inflammation [3]. Further explanation is needed with regard to mechanisms underlying such brain injuries that are associated with ventilator-weaning difficulties, early rehabilitation being impossible, prolonged fatigue and increased care-related problems.

Brain MRI investigations have revealed the severity of injuries in such patients [3]. When damage is diffuse, standard cerebrospinal fluid (CSF) analyses have found inflammatory profiles [4]. It has been suggested that either severe hypoxia or immune-mediated inflammation occurred in the CNS, although neither oxygen nor steroid administration completely reduced dysfunction of a similar phenotype in other similar settings (reference [SR2, SR3]). It was therefore postulated that the study of brain repair factors that are upregulated through hypoxia and/or inflammation, such as erythropoietin (EPO) [5], and the analysis of small molecules (<2000 Da) by CSF metabolomics might help to characterize brain-specific suffering during COVID in ICU patients.

METHODS

Patients

The study was approved by the Ethical Committee of our hospital. Informed consent was obtained from all participants. Patients had a COVID-related ARDS without previous medical history of neurological disease or addiction (see criteria in Supporting information SI 1). The delirium studied herein is not the hypoxia-related neurological status observed on admission but the status observed at sedation tapering after re-oxygenation in accordance with updated nomenclature [1]. In addition to unmanageable agitation, patients demonstrated hyperventilation (>40/min) with low tidal volume and hypoxaemia that required further prolonged anaesthesia. Controls were ICU patients with septic conditions detected as COVID negative. Controls and COVID+ were prescribed similar anaesthesia/sedation as well as identical enteral feeding. At discharge, an alimentary inquiry was carried out to categorize patients as having a Mediterranean or a Western diet pattern.

Imaging

Studies were conducted as in Kremer et al. [3]: images were recorded first at diagnosis of resistant delirium and secondly at 3-month discharge whereas, in controls, images were recorded once before lumbar puncture (LP).

Biological dosages and metabolomics

In the CSF, interleukin 6 (IL-6) was assessed with a Human IL-6 ELISA Kit (Invitrogen Thermo Fisher Scientific) and EPO with a monoclonal anti-EPO antibody (Siemens). Half of the patients underwent the LP within the first 2 weeks of admission (early assessment), and half later (late assessment).

Cerebrospinal fluid samples were stored at −80°C and analyzed by liquid chromatography (LC) coupled with high resolution mass spectrometry (HRMS) using a DioneX Ultimate 3000 (Thermo, MA, USA) coupled to a Q-TOF Impact II (Bruker, Bremen, Germany). Details of sample handling and analysis are available in Supporting information SI 2. The spectrometer was operated with an electrospray ionization source (method A) and an atmospheric pressure photoionization source (method B). Detailed information on methods is available in Supporting information SI 3.

Statistical analyses

The Wilcoxon rank sum test (Mann–Whitney *U* test) was used for comparisons of quantitative variables and the Fisher exact test for binary variables. For the metabolomics assessment, only compounds found in 80% of group samples were selected. The features of interest were selected based on the nonparametric Wilcoxon rank sum test (p value <0.05) and fold change ≥2 (absolute value) as described previously [6].

RESULTS

Amongst the 89 ICU COVID+ admitted (Supporting information SI 4), 10 were included because they fulfilled inclusion criteria, and so were seven septic controls.

At admission, demographic, clinical and laboratory features were balanced between groups although COVID+ were more hypoxic and displayed more inflammation (Supporting information SI 5). The admission SARS-CoV-2 RNA load in lungs of 6.16 (5.55;

6.54) log copies/reaction decreased to a median value of 2.27 (1.54; 3.79) log copies/reaction when LP was performed. Typical MRI aspects recorded in COVID+ are depicted in Supporting information SI 6.

Cerebrospinal fluid EPO concentrations were lower in COVID+: 1.73 (1.6; 2.06) vs. 3.04 (2.9; 3.91) mIU/ml, $p < 0.01$. They did not differ whether LP was performed early after admission or later (1.77 [1.59; 1.91] vs. 1.7 [1.62; 2.11] mIU/ml), although both were lower than in controls (3.04 [2.9; 3.91] mIU/ml, $p = 0.03$).

At ICU discharge, no patient experienced neurological defects, but all COVID+ complained of depression, anxiety, post-traumatic symptoms (sleeping troubles, nightmares) and fatigue; these signs were still present in 100% of survivors at 3-month discharge.

Metabolomics screening of CSF

Univariate analysis disclosed 84 increased and 153 decreased compounds in COVID+ (Supporting information SI 7). Only 48 compounds could be assigned a molecular formula (Supporting information SI 8). The putative compounds with a significant increase were foodborne molecules, molecules originating from alcoholic beverages, micro-pollutants (diethanolamine) and miscellaneous compounds. Decreased molecules were incomplete breakdown products of protein catabolism, foodborne molecules (olomoucine, (R)-glabridin, diacylglycerols) and miscellaneous compounds (including spectinomycin and irbesartan).

ChemRICH analysis of CSF displayed 46 chemical class clusters. Four clusters showed differences between COVID+ and controls: dipeptides, sesquiterpenes, ethanolamines and carbocyclic acids (Supporting information SI 9, Panel A & Panel B, SI 10 & SI 11).

DISCUSSION

Severe neurological effects exist in ICU-treated COVID+ who developed unexpectedly a resistant delirium after life-saving re-oxygenation for ARDS. Amongst the various neurological associations between COVID and ARDS, the most worrying was this delirium, which occurred at a lower frequency than other neurological associations [7]. In the absence of a proven pathophysiological mechanism, this development gives cause for concern [8]. Our data underscore the absence of complete brain injury repair and the possibility of underlying silent conditions as supplemental risk factors for sequelae.

This delirium is unlikely to be the exclusive consequence of direct SARS-CoV-2 damage since no SARS-CoV-2 RNA was detected in the CSF. In contrast to animal models (reference [SR4]), the presence of the virus in the human brain has seldom been reported [SR5]. In arteries, the virus triggers endotheliitis [SR6]: in large arteries this has caused extended stroke [SR7], whilst it should have resulted in diffuse multifocal ischaemic areas in smaller ones, as reported in other contexts of profound hypoxia [SR8]. MRI showed micro-bleeds and inflammation, suggesting additional mechanisms of disease [SR9]. In COVID+, the admission hypoxia was likely to have reached the threshold promoting brain remodelling and tissue protection through the upregulation of EPO and vascular endothelial growth factor [SR10, SR11]. EPO stimulates endothelial cells, which increase endothelin-1 secretion, thereby further exacerbating local ischaemia and inflammation [SR12]. An EPO receptor expression also exists in neurons within selected locations [SR13] in both a hypoxia- and a cytokine-dependent inducible manner. However, it is difficult to conclude that a 'cytokine storm' explains a long-lasting delirium when this was absent in controls. The blood–brain barrier was probably altered in COVID+ with an increased local IL-6 production; this will have augmented the risk of systemic inflammation impaction on CNS structures [SR14]. However, CSF metabolomics indicated that foodborne spectinomycin was present at a lower concentration in COVID+ than in controls. Similarly, irbesartan, which had not been administered, was detected in higher amounts in controls, although this molecule is not meant to spread in the CSF [SR15]. These data confirm that sepsis-associated systemic inflammation is a mechanism driving an efflux of substances from plasma into CSF in controls rather than in COVID+. Our findings tend to support the recently described 'bradykinin storm' theory with diffusion of small molecules [SR16]. The lack of proper brain healing is striking because the level of EPO indicated a prolonged defective brain repair. This suggests a persistent process of the EPO pathway upregulation resembling the SARS-CoV-2-induced inhibition of heme structures [SR17]. An alternative explanation for incomplete brain injury repair in COVID+ is that proposed for ARDS-triggered acute pulmonary fibrosis [9]. ARDS requires support of high-oxygen concentrations. Oxygen weakens local pulmonary anti-inflammatory mechanisms such as those related to the adenosine A_{2A} receptor—hence the possibility of exacerbation of acute tissue injury, even in the brain [SR18]: this may explain why COVID+ only partially recover late after discharge.

COVID delirium may also result from an unusual exacerbation of persistent chronic but silent brain inflammation by acute-onset inflammation. With the input of CSF metabolomics, the focus was on substances related to lifestyle factors known to impact on microglia inflammation, which paves the way for some brain diseases [SR14]. Obesity, diabetes, tobacco consumption or alcohol intake are associated with chronic tissue inflammation and the outbreak of severe forms of community-acquired respiratory infections [SR19] including pulmonary COVID [SR20]. Amongst molecules modified in COVID+, annotations suggested that the presence of foodborne molecules originating from industrialized beverages, ultra-processed food and roasted meat was increased. Diethanolamine, a molecule structurally related to choline and a ubiquitous micro-pollutant found in cosmetics [SR21], inhibits the transport of choline with impact on the phospholipid metabolism [SR22]. In COVID, choline sustains macrophage activation and diethanolamine could affect the macrophage response, thereby exacerbating the infection [SR23]. Incomplete protein catabolism was also common in COVID+; this

suggests the possibility of chronic activation of some specific proteases in COVID+. On scrutinizing the diet of COVID+, a predominance of roasted meat and a few root vegetables was found. This feature of our local diet may explain the presence of micro-pollutants. Such a link between a diet lacking some molecules and a higher risk of COVID is possible, since low concentrations of glabridin (an isoflavonoid with anti-inflammatory, neuroprotective and antimicrobial properties) would facilitate the development of viral infection [SR24]. The ChemRICH analysis indicated changes in concentrations of sesquiterpenes in COVID+. Their relative concentrations in CSF suggest a possible unbalanced effect on the nuclear factor κB (NF-κB) pathway [SR25]. Thus, parthenolide, a natural sesquiterpene, has been associated *ex vivo* in brain cells and *in vivo* in SARS-infected mice with decreased inflammation and increased survival linked to NF-κB inhibition [10] whereas alantolactone, a natural sesquiterpene lactone inhibiting the IkappaB kinase beta kinase activity [SR26], may have an opposite effect.

Our data suggest a pathophysiological link between COVID ARDS and brain inflammation. Whether EPO supply would ameliorate neuro-COVID remains questionable, notably because EPO has proved beneficial in ischaemic stroke but deleterious in other settings ([SR27, SR28]). This therefore rather raises the question of brain injury prevention, and the need for conservative oxygen therapy in patients at risk of neuro-COVID. Closer attention should usefully be devoted to lifestyle and environmental conditions as aggravating factors [SR29].

Some COVID+ are at risk of a specific delirium. Imperfect brain repair after re-oxygenation and lifestyle factors might influence long-lasting brain injuries in a context of foodborne micro-pollutants.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Francis Schneider: Conceptualization (lead); formal analysis (equal); funding acquisition (lead); investigation (lead); methodology (equal); project administration (equal); resources (lead); software (supporting); supervision (equal); validation (lead); visualization (lead); writing original draft (lead); writing review and editing (lead). Arnaud Agin: Conceptualization (equal); data curation (equal); formal analysis (equal); funding acquisition (supporting); investigation (equal); methodology (equal); project administration (supporting); resources (supporting); software (equal); supervision (equal); validation (lead); visualization (equal); writing original draft (equal); writing review and editing (equal). Mathieu Baldacini: Conceptualization (equal); Data curation (equal); formal analysis (supporting); funding acquisition (supporting); investigation (lead); methodology (supporting); project administration (equal); resources (supporting); software (equal); supervision (supporting); validation (equal); visualization (equal); writing original draft (equal); writing review and editing (equal). Loïc Maurer: Conceptualization (supporting); data curation (equal); formal analysis (equal); funding acquisition (supporting); investigation (equal); methodology (lead); project administration (supporting); resources (supporting); software (equal); supervision (supporting); validation (lead); visualization (equal); writing original draft (supporting); writing review and editing (supporting). Maleka Schenck: Conceptualization (equal); data curation (equal); formal analysis (supporting); investigation (equal); methodology (supporting); validation (equal); visualization (equal); writing original draft (supporting). Mathieu Alemann: Conceptualization (equal); data curation (equal); formal analysis (equal); methodology (equal); validation (equal); writing original draft (equal). Morgane Solis: Data curation (equal); formal analysis (equal); investigation (equal); writing original draft (equal). Julie Helms: Data curation (equal); formal analysis (supporting); investigation (supporting); methodology (supporting); writing original draft (equal). Claire Villette: Formal analysis (lead); investigation (equal); methodology (supporting); supervision (equal); validation (lead); writing original draft (equal). Thierry Artzner: Data curation (supporting); formal analysis (equal); investigation (equal); methodology (equal); validation (equal); writing original draft (equal). Stéphane Kremer: Conceptualization (lead); data curation (equal); formal analysis (equal); investigation (lead); methodology (equal); supervision (equal); validation (lead); visualization (equal); writing original draft (equal); writing review and editing (equal). Dimitri Heintz: Conceptualization (lead); data curation (equal); formal analysis (lead); funding acquisition (equal); investigation (lead); methodology (lead); project administration (lead); resources (equal); software (equal); supervision (lead); validation (lead); visualization (equal); writing review and editing (lead).

DATA AVAILABILITY STATEMENT

All data are available for collaborative studies with qualified investigators.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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