Covid-19 patients' brains show alzheimer's-like signaling

Alison Parker

Parker A. Covid-19 patients' brains show alzheimer's-like signaling. J Neuropathol. 2022;2(1):3-4

ABSTRACT

COVID-19 patients have multi-system organ failure that affects not just the lungs, but also the cardiovascular, neurological, and other systems. The pleiotropy and complexity of organ system failures complicate COVID-19 patient care and contribute to the pandemic's morbidity and mortality to a large extent. Acute Respiratory Distress Syndrome (ARDS) is the most prevalent symptom of severe COVID-19 infection (ARDS). When SARS-CoV-2 infects lung cells, it causes severe inflammation in the lungs, which leads to respiratory failure. Hypoxia, hypotension, increased inflammatory state, Angiotensin-Converting Enzyme 2 (ACE2) receptor downregulation, endogenous catecholamine adrenergic stimulation, and direct viral-induced myocardial injury are all examples of cardiac symptoms. Patients with underlying cardiovascular illness or comorbidities, such as congestive heart failure, hypertension, diabetes, or pulmonary disease, are also more vulnerable.

A third of COVID-19 patients have neurological symptoms, such as headaches, impaired consciousness, and paresthesia's, in addition to respiratory and cardiac signs. 8 There have also been reports of brain tissue edema, stroke, neuronal degeneration, and neuronal encephalitis. Diffuse neural inflammatory indicators were discovered in >80% of COVID-19 patient brains in a recent investigation, processes that may contribute to the observed neurological symptoms. Hyposmia and hypogeusia, or the loss of the ability to smell and taste respectively, are two more common signs of SARS-CoV-2 infection. Hyposmia has been documented in early-stage Alzheimer's disease (AD), 3 and AD type II astrocytosis has been seen in COVID-19 patients' neuropathology investigations.

The ACE2 receptor, which is extensively expressed in pericytes of the human heart and epithelial cells of the respiratory tract, kidney, intestine, and blood vessels, is believed to be the cause of systemic failure in COVID-19 individuals. Although it is unknown if the SARS-CoV-2 virus directly infects neurons in the brain, ACE2 is expressed in the brain, particularly in the respiratory centre and hypothalamus in the brain stem, the thermal centre, and cortex, making these tissues more sensitive to viral invasion. Inflammatory reactions and oxidative stress in various organs and tissues are the principal effects of SARS-CoV-2 infection. It has recently been discovered that the high neutrophil-to-lymphocyte ratio seen in COVID-19 patients is linked to high levels of reactive oxygen species (ROS) and ROS-induced inflammation.

Key Words: *Cardiac rehabilitation; Core components; Guidelines; Heart valve surgery; Heart valve replacement*

SHORT COMMUNICATION

Oxidative stress and inflammatory signaling pathway indicators, as well as assessments of Alzheimer's disease (AD)-linked signaling biochemistry, were evaluated in brain lysates from control and COVID-19 patients. Co-immunoprecipitation/immunoblotting of the brain lysates revealed post-translational alterations of the ryanodine receptor/calcium (Ca2+) release channels (RyR) on the endoplasmic reticula (ER), which have been associated to AD [1].

The COVID Biobank at Columbia University provided de-identified human heart, lung, and brain tissue. The brain samples came from the mesial temporal lobe, while the cerebellum samples came from the lateral hemisphere of the cerebellar cortex. For sample collection and maintenance, the Columbia University Biobank follows standard operating procedures, quality assurance, and quality control. There were no neurological abnormalities, cardiovascular illness, or pulmonary disease in age- and sex-matched controls [2].

Tissues (50 mg) were homogenized in 0.25 ml of 10 mM Tris maleate (pH 7.0) buffer with protease inhibitors using a Dounce homogenizer (Complete inhibitors from Roche). The protein concentrations of the supernatants were measured using the Bradford assay after centrifugation at 8000 g for 20 minutes. Tissue proteins (20 g) were separated by 4 percent to 20% Sodium Dodecyl Sulphate Polyacrylamide Gel Electrophoresis (SDS-PAGE) and immunoblots were generated using the following antibodies: pSMAD3 (Abcam, 1:1000), SMAD3 (Abcam, 1:1000), AMPK (Abcam, 1:1000), tau (Abcam, 1:1000). (Thermo Fisher, 1:1000)

At 4°C, 0.1 mg tissue lysates were treated with buffer or 10 M Rycal (ARM210). Anti-RyR2 specific antibody (2 g) was used to immune precipitate RyR2 from 0.1 mg lung, heart, and brain in 0.5 ml of a modified radioimmune precipitation assay buffer (50 mm Tris-HCl, pH 7.2, 0.9% NaCl, 5.0 mm NaF, 1.0 mm Na3VO4, 1% Triton X-100, and protease inhibitors; RIPA) overnight at 4°C The peptide CKPEFNNHKDYAQEK, which corresponds to mouse RyR2 amino acids 1367–1380 with a cysteine residue added to the amino terminus, was used to create an affinity-purified polyclonal rabbit antibody specific for RyR2 [3]. The immune complexes were incubated for 1 hour at 4°C with protein A-Sepharose beads (Sigma) before being washed three times with RIPA. On SDS-PAGE gels, the immune precipitates were size-fractionated.

RyR2 was immune precipitated from 1.5 mg of tissue lysate in 1.0 ml of a modified RIPA buffer overnight at 4°C using an anti-RyR2 specific antibody (25 g). The immune complexes were incubated for 1 hour at 4°C with protein A-Sepharose beads (Sigma), then washed three times with RIPA buffer, then twice with ryanodine binding buffer (10 mM Tris-HCl, pH 6.8, 1 M NaCl, 1% CHAPS, 5 mg/ml phosphatidylcholine, and protease inhibitors). For 1 hour at 37°C, immune precipitates were incubated in 0.2 ml binding buffer containing 20 nM [3H] ryanodine and either 150 nM or 20 m free Ca2+. Filtered samples were diluted with 1 ml of ice-cold washing buffer (25 mm Hepes, pH 7.1, 0.25 m KCl) and diluted with 1 ml of ice-cold washing buffer (25 mm Hepes, pH 7.1, 0.25 m KCl).

For lysis, 20 mg of tissue was suspended in 200 litres of ice-cold phosphate-buffered saline/0.5% NP-40, pH6.0. A Dounce homogenizer was used to homogenise the tissue in 10 to 15 passes. To remove any insoluble material, samples were centrifuged at 8000 g for 15 minutes at 4°C. The supernatant was poured into a new tube. The samples were deproteinized by adding one volume of ice-cold 100 percent (w/v) trichloroacetic acid (TCA) to five volumes of sample and vortexing quickly to thoroughly mix everything together. Samples were centrifuged at 12,000 g for 5 minutes at 4°C after being incubated for 5 minutes on ice, and the supernatant was transferred to a new tube. The samples were neutralised by adding NaHCO3 to the supernatant and vortexing briefly. The samples were centrifuged at 15,000 rpm for 15 minutes.

The quantity of Kynurenic Acid (KYNA) in brain lysates was measured

Editorial office, Journal of Neuropathology, China

Correspondence: Alison Parker, Editorial office, Journal Of Neuropathology, China, E-mail neuropathology@pulsusinc.com

Received: 04 January 2022, Manuscript No. PULNP-22-4221; Editor assigned: 06 January 2022, PreQC No. PULNP-22-4221(PQ); Reviewed: 20 January 2022, QC No. PULNP-22-4221(QC);Revised: 20 January 2022, Manuscript No. PULNP-22-4221(R); Published: 24 January 2022; DOI: 10.37532/pulnp.2022.2(1).3-4

using an Enzyme-Linked Immunosorbent Assay (ELISA) kit (ImmuSmol). Briefly, 50 l of samples were placed in a microtiter plate intended to extract KCNA from the samples. To derivatize the materials, an acylation reagent was applied for 90 minutes at 37°C. After derivatization, 50 l of the prepared standards and 100 l of the samples were pipetted into the KYNA microtiter plate's corresponding wells. All wells were filled with KYNA Antiserum, and the plate was incubated at 4°C overnight. The enzyme conjugate was added to each well after the plate had been washed four times. The plate was shaken at 500 rpm for 30 minutes at room temperature. The enzyme substrate was applied to all of the samples.

A PKA activity kit was used to measure PKA activity in brain lysates (Thermo Fisher, EIAPKA). Samples were placed in a microtiter plate with an immobilized PKA substrate that was phosphorylated by PKA in the presence of ATP. After 2 hours of incubation with ATP at room temperature, the plate was treated for 60 minutes with the phospho-PKA substrate antibody. After washing the plate with wash buffer, each well was filled with goat anti-rabbit IgG Horseradish Peroxidase (HRP) conjugate. The plate was aspirated, cleaned, and TMB substrate was added to each well before being incubated at room temperature for 30 minutes. The absorbance at 450 nm was measured using a plate reader. A standard curve was used to compare the sample signals.

The CycLex CaM kinase II Assay Kit was used to measure CaMKII activity in brain lysates (MBL International). Samples were placed in a microtiter plate with an immobilized CaMKII substrate, which is phosphorylated by CaMKII in the presence of Mg2+ and ATP. After 1 hour of incubation in kinase buffer containing Mg2+ and ATP at room temperature, the plate was washed and incubated for 60 minutes with the HRP conjugated anti-phospho-CaMKII substrate antibody. The plate was aspirated, cleaned, and TMB substrate was added to each well before being incubated at room temperature for 30 minutes. The absorbance at 450 nm was measured using a plate reader. A standard curve was used to compare the sample signals.

SARS-CoV-2 infection is linked to TGF signaling activation and oxidative stress, according to our findings. The neuropathological mechanisms that cause tau hyper phosphorylation, which is linked to Alzheimer's disease, were also found to be active in COVID-19 patients. RyR2 showed a "leaky" phenotype in COVID-19 brains, which can lead to cognitive and behavioral problems [4].

Leaky RyR2 channels could be a therapeutic target for ameliorating some cognitive deficits associated with SARS-CoV-2 infection and protracted COVID. COVID-19 neuropathology includes AD-like characteristics.

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