HHS Public Access

Author manuscript

Pain. Author manuscript; available in PMC 2023 March 23.

Published in final edited form as:

Pain. 2020 November ; 161(11): 2431–2433. doi:10.1097/j.pain.0000000000002050.

Clinical significance of angiotensin-converting enzyme 2 receptors for severe acute respiratory syndrome coronavirus 2 (COVID-19) on peripheral small-fiber sensory neurons is unknown today

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During the first months of the global severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2/COVID-19) pandemic, medical care appropriately focused on urgent care and public health measures. Acute respiratory distress has been the greatest concern, with initial mortality rates improving from practical experience, better resourcing, and outcomes analyses. It has been too early to elucidate the cellular pathways of pulmonary and other organ damage or to characterize the later and long term sequelae of serious COVID-19.

Severe acute respiratory syndrome coronavirus 2 RNA virus enters human host cells through coronavirus-associated receptors and factors (SCARFs), including cleaving transmembrane proteases angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2). SCARFs are widely expressed, including in lymphoid, renal, gastrointestinal, and mucosal cells, reproductive organs, and vascular endothelium. Multiorgan involvement in COVID-19 is well documented, particularly in children.[12] However, clinical involvement does not imply local cellular infection; pathological studies so far highlight the nonspecific effect of profound inflammation and hypoxia/ischemia.[24,37]

Neuropathological analyses from patients with COVID have so far not included the human dorsal root ganglion (hDRG). Now, in this *PAIN* issue, Shiers and coworkers document elegantly that 1/4th of hDRG neurons express low levels of mRNA for several SCARFs including ACE2, and apparently contain ACE2 protein.[35] The labeled cells are small-fiber sensory neurons coexpressing the MAS-related G-protein-coupled receptor D (Mrgprd) that transmits nociceptive signals from the skin.[41] The team deserves applause for obtaining living human tissues (and analyzing 816 neurons from 3 patients), given the barriers to anatomic donation. Donations of human tissue have been dwindling for decades because of insurer and cost disincentives and inadequate appreciation of their value.[37]

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Conflict of interest statement

The author has no conflicts of interest to declare.

Neuroradiologic advances give false impressions that pathogenesis is always discoverable noninvasively during life. The analyses by Shiers et al.[35] were adequately powered, and they comprehensively studied multiple SCARFs and measured ACE2 protein as well as mRNA.

However, mRNA expression was low and only in a minority of hDRG cells,[35] so whether or not this conveys susceptibility to SARS-CoV-2 infection is unknown. Granted, mRNA levels do not always predict protein levels, stability, or distribution, and comorbidities can enhance expression.[10] The presence of viral receptors is certainly plausible, given that "small fibers" are front-line responders to infection. Evolutionarily ancient small-diameter DRG and autonomic neurons retain pluripotent defensive capabilities; sensing pain and itch are just 2 muskets in the small-fiber militia. To scan for internal threats, sensory small-fibers expose their cell bodies to infection in ganglia with fenestrated capillaries and extend unsheathed axon terminals to body surfaces. They densely innervate our skin and internal mucosa (which still contact the external world), and the mucosa are nearly always involved in severe COVID-19. Small fibers modulate immunocytes, blood vessel linings, and even bones and bone marrow. But, such a broad range of innervation targets leaves small-fiber neuropathy (SFN) patients with subjective nonspecific symptoms. Most SFN illnesses remain undiagnosed. Patients never complain "My C fibers are killing me!"

Is there evidence of neuronal penetration (infection) of small fibers by SARS-CoV-2? ACE2 is widely expressed throughout the body for a different purpose, cleaving circulating proinflammatory angiotensinogen II (ANG II) into smaller anti-inflammatory mediators. When SARS-CoV-2 cross reacts with ACE2, it inhibits ANG II binding and cleavage, leaving body-wide elevated levels that increase blood pressure and inflammation and damage cells including blood-vessel linings. These indirect effects of SARS-CoV-2 binding appear to be the biggest acute problem, with general autopsy studies reporting hypoxic/ischemic multiorgan damage (sepsis) causing organ malfunction, hemorrhage, and sometimes infarction and necrosis.[3,31] Despite brain symptoms, confusion, seizures, and encephalitis, reported in 10% to 36% of severe COVID-19 illnesses, postmortem brains show little or no SARS-CoV-2 RNA and protein (also true in lung and respiratory epithelia).[17] Eighteen consecutive brain autopsies of polymerase chain reaction–confirmed patients found universal acute hypoxic injury and neuronal loss without thrombi or vasculitis, but no neuronal infection.[36] Two brains had rare perivascular lymphocytic foci, and 1 had focal leptomeningeal inflammation. Quantitative reverse transcription polymerase chain reaction for SARS-CoV-2 nucleocapsid protein detected low levels in 5 patients, but immunohistochemistry detected no protein in neurons, glia, endothelium, or immune cells. And, nonspecific staining in the choroid plexus of 7 patients could have reflected circulating blood-borne virus.[36] The prolonged comas and slow brain recoveries are increasingly linked to nonspecific effects of long exposures to sedatives and suboptimal oxygenation for hours, days, or weeks.[29] Measuring plasma markers from 47 patients with COVID-19 yielded evidence of central nervous system astrocyte activation in those with moderate and severe illnesses.[19]

In the peripheral nervous system, to date, myopathy is the most prevalent post–COVID-19 neuromuscular disorder,[15,32] but neuropathy can develop,[8,27,34] with Guillain–Barré syndrome motor neuropathies best recognized so far.[9,14,32,40] Guillain–Barré syndrome is

attributed to immune cross-reactivity between infectious and neural antigens (molecular mimicry). Given the discovery that small fibers bear ACE2 epitopes, could COVID-19 trigger corresponding small-fiber autoimmunity?[35] Although no cases are yet reported, this appears plausible. Large-fiber sensory Guillain–Barré syndrome affecting the hDRG can develop,[27] along with apparently autoimmune SFN incident to viral infections and immunization.[2,20,22,23,34,39] COVID-19 cranial neuropathies sometimes include the 4 somatosensory ganglia (V, VII, IX, and X), although given coexisting leptomeningeal enhancement, the ganglionic origin cannot be inferred.[4,5,7,8,16,27,34]

Herpes zoster (shingles) proves that viruses can directly infect hDRG neurons to cause neuropathic pain. But there is no direct proof of PNS neuronal infection by SARS-CoV-2. A confirmed COVID-19 patient with sudden new bilateral “excruciating” leg pain and paresthesias later developed mild leg weakness. Because MRI and cerebrospinal fluid demonstrated spinal cord and proximal nerve root involvement, the origin of his painful polyradiculoneuritis is uncertain.[6] Even if hDRG infectivity was demonstrated in a few cases, larger surveys would be needed to establish the prevalence. The question of COVID-19 small-fiber infectivity is important, given that sensory small fibers receiving input from laryngeal and tracheal lining cells for airway defense, and their postsynaptic central contacts can trigger pulmonary edema and hypoxia.[30] Small-fiber neuropathy has been postulated to contribute to the gastrointestinal (GI) complications detected in 45% of the 141 consecutive patients admitted to an intensive care unit (ICU) for severe COVID-19 between March 13, 2020, and April 12, 2020.[18] GI motility is small-fiber controlled, and the presence of dysmotility symptoms is correlated highly with the presence of biopsy-confirmed SFN at the Massachusetts General Hospital.[38] Half of COVID-19 ICU patients in this study[18] had dysmotility, typically severe enough to require feeding by nasogastric or orogastric tube. Bowel tissue from 4 operated patients showed nonspecific ischemia and necrosis and micro-vessel thrombosis.[18] Unfortunately, no mucosal samples were sent for the pathological assessment of small-fiber integrity. Other indirect evidence, the common symptoms of reduced taste and chemesthesis (mouth sensitivity) for capsaicin and menthol[28] and rare symptoms such as diffuse or limb pain, dysautonomia,[32] and classic distal sensory loss, also raises the possibility of sensory/small-fiber involvement. It is unclear whether there are preferential local effects of the excess ACE2 no longer cleaved by COVID-occupied ACE-2. If so, the DRG, and perhaps sensory axons, may be vulnerable.

We have not yet begun to characterize the full spectrum of post-COVID neuropathies. As in the central nervous system, many will have nonspecific causes. Peripheral neurons, particularly small fibers, are very long and thus vulnerable to hypoxia.[26] Prolonged and ICU hospitalization conveys risk for nerve compressions, trauma, nutritional depletion, and neurotoxic treatments.[8] The underlying risks for severe COVID-19, eg, diabetes, smoking, obesity and cardiovascular limitations, and age itself, are independent risks for SFN (reviewed in Ref. 26).[33] Two large studies of neurological consequences in children with COVID-19 multisystem inflammatory syndrome report muscle weakness and reduced reflexes, and in 1 study, all 4 requiring ICU admission had evidence of neuropathy.[1,12] New-onset SFN in healthy children, adolescents, and young adults often appears dysimmune, with many linked to shortly preceding viral infections.[11,25]

The new consensus recommendations for research diagnosis of initially idiopathic SFN require confirmation by PGP9.5-immunolabeled skin biopsy.[13] So, clinicians with suspected COVID-incident SFN should contact accredited academic clinical neuroskin biopsy labs for instructions on local biopsy, Zamboni fixation, and shipping (also see https://neuropathycommons.org/). Blood-test elimination of other more common causes of SFN[21] and sensory nerve conduction are ideal. Biopsies should be costudied for inflammatory cells and ideally SARS-CoV-2. Neuroautopsies should include the spinal cord and PNS. Methodologically sophisticated university labs can also access metagenomic and immune repertoire sequencing techniques helpful in identifying emerging neuroinfectious agents for which commercial testing is limited.

In summary, the report of Shiers et al.[35] is an important step, but it does not prove COVID-19 preferential damage to hDRG small-fiber neurons. Instead, it indicates the need for greater awareness of small-fiber neuropathy and surveillance and investigation of potential COVID-incident SFN.

Acknowledgements

Funded in part by Public Health Service R01NS09653 and private foundation grants to A.L. Oaklander.

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