INSIDE VIEW

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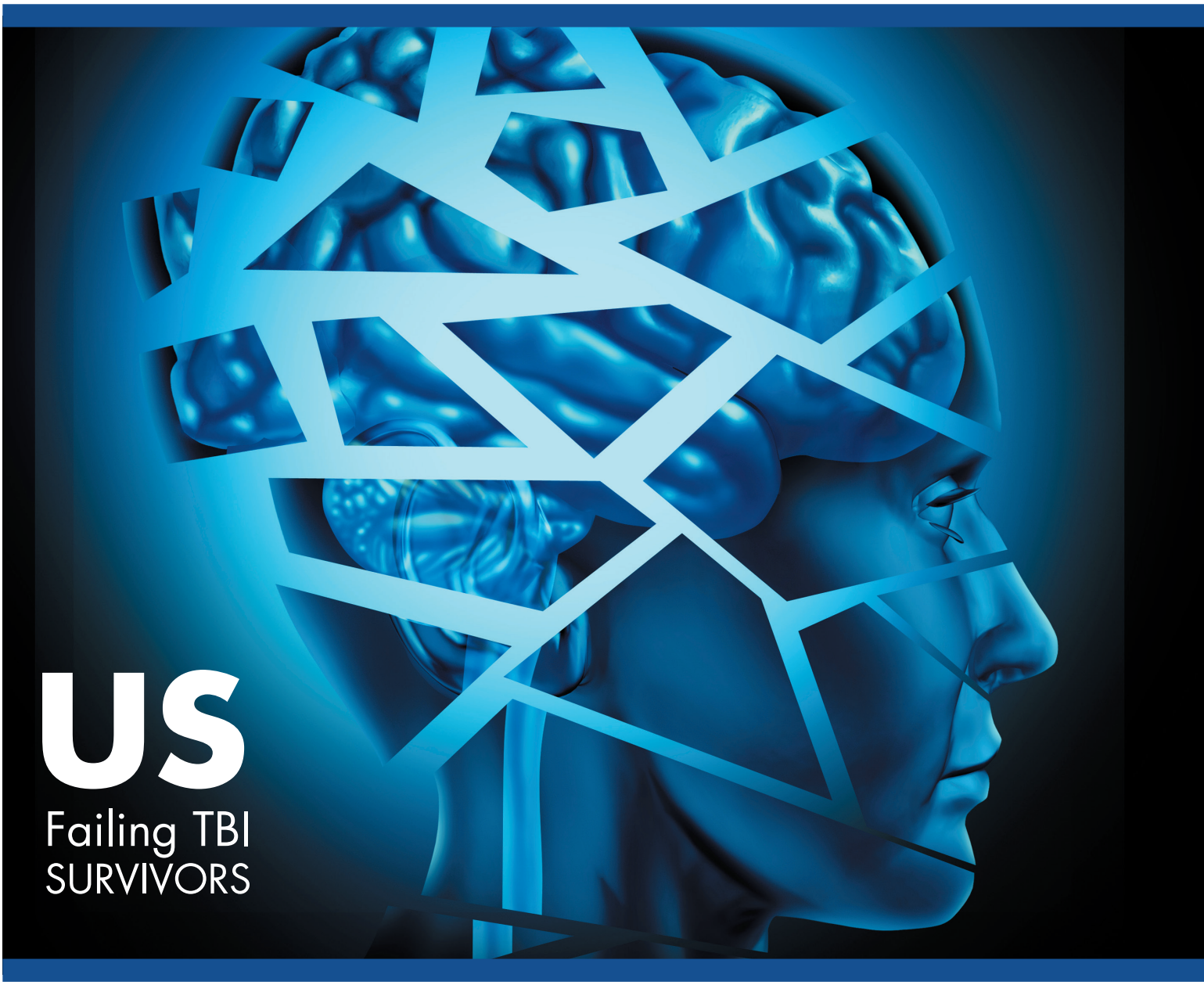

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CNS California Facilities Awarded a Three-Year Accreditation by CARF International

Centre for Neuro Skills (CNS), a premier provider of treatment for traumatic and acquired brain injury, announced that its California facilities have been accredited for a period of three years by CARF International (formerly Commission on Accreditation of Rehabilitation Facilities). CARF International is an independent, nonprofit accrediting body whose mission is to promote the quality, value and optimal outcomes of services through a consultative accreditation process and continuous improvement that centers on enhancing the lives of persons served. The accreditation extends through Dec. 31, 2024.

CARF-accredited organizations identify leadership that embraces the values of accountability and responsibility while demonstrating corporate social responsibility.

"What sets CNS apart from other rehabilitation facilities is our focus on brain injury and/or stroke, and individualized treatment for each patient, with the end goal of maximizing independence and quality of life," said David Harrington, president and chief operating officer of CNS. "The CARF accreditation process is very rigorous, and the report truly captures the heart and culture of CNS – the dedication, inspiration, integrity and innovation toward our patients, their families, our colleagues, and the field of rehabilitation. CNS is honored by the high praise in the surveyors' accreditation report."

During the rigorous on-site peer review process, CNS demonstrated to a team of surveyors its dedication and commitment to offering programs and services that are measurable, accountable and of the highest quality.

Areas of strength noted include:

- CNS has an extraordinary discharge process with a level of detail and coordination throughout, incorporating all disciplines, resources, and coordination of appointments and ongoing areas of need in all California locations.
- All locations in California quickly adapted to the COVID-19 pandemic by utilizing telehealth and developing protocols consistent with government guidelines, with capacity for rapid testing on-site for both staff members and patients.
- CNS' facilities are well designed, spacious and nicely furnished. At the clinics, patients are happy with the opportunities for rehabilitation, while those in the residential treatment enjoy desirable neighborhoods with easy access to shipping, restaurants, banking and public transportation. All the apartments are in a gated, secure community, with access to a pool and fitness center.
- The Bakersfield location was praised for its compassion and support for its clinician teams, who have demonstrated incredible longevity, dedication and compassion for the jobs that they do.
- Patients, family members and referral sources report a very high level of satisfaction with the quality and intensity of services in both the residential and outpatient settings. Their comments include: "It's a good feeling in my heart when I refer to them," "I would choose CNS for myself," "They have changed my life," and "No one else could do all of this for our family."

Programs awarded accreditation to CNS' California facilities include:

San Francisco Bay Area (Emeryville)

- Interdisciplinary Outpatient Medical Rehabilitation: Brain Injury Specialty Program (Adults)
- Interdisciplinary Outpatient Medical Rehabilitation: Brain Injury Specialty Program (Children and Adolescents)
- Interdisciplinary Outpatient Medical Rehabilitation: Stroke Specialty Program (Adults)
- Residential Rehabilitation: Brain Injury Specialty Program (Adults)
- Residential Rehabilitation: Stroke Specialty Program (Adults)

Bakersfield

- Interdisciplinary Outpatient Medical Rehabilitation: Brain Injury Specialty Program (Adults)
- Interdisciplinary Outpatient Medical Rehabilitation: Brain Injury Specialty Program (Children and Adolescents)
- Interdisciplinary Outpatient Medical Rehabilitation: Stroke Specialty Program (Adults)

Los Angeles Area (Woodland Hills)

- Residential Rehabilitation: Brain Injury Specialty Program (Adults)
- Residential Rehabilitation: Stroke Specialty Program (Adults)
- Los Angeles Area (Tarzana)
- Interdisciplinary Outpatient Medical Rehabilitation: Brain Injury Specialty Program (Adults)
- Interdisciplinary Outpatient Medical Rehabilitation: Brain Injury Specialty Program (Children and Adolescents)
- Interdisciplinary Outpatient Medical Rehabilitation: Stroke Specialty Program (Adults) ■

2022-23 Calendar of Events

May

13-19
ASNR 2022 Symposium and Annual Meeting
New York, NY
asnr.org/events/upcoming-meetings/asnr/

15-18
2022 IRSG Annual Conference
Baltimore, MD
irsghome.org/

Jun

6-7
12th Annual Traumatic Brain Injury Conference
Washington, D.C.
tbiconference.com/home/

26-28
12th Annual Traumatic Brain Injury Conference
Washington, D.C.
tbiconference.com/home/

26-29
BIA of Pennsylvania Annual Conference
Lancaster, PA
biapa.org/annualconference/

Sep

21-24
Fourth International Conference on Pediatric Acquired Brain Injury
New York, NY
internationalbrain.org/meetings-and-events/virtual-conference-2021

21-24
34th Annual Conference on Medical and Legal Issues in Brain Injury
New York, NY
internationalbrain.org/meetings-and-events/2022-legal-and-medical-issue-in-brain-injury

Nov

8-11
ACRM Annual Conference
Chicago, IL
acrm.org/meetings/

Mar 2023

29-1
14th Biennial World Congress on Brain Injury
Dublin, Ireland
internationalbrain.org/meetings-and-events/ibia-world-congress

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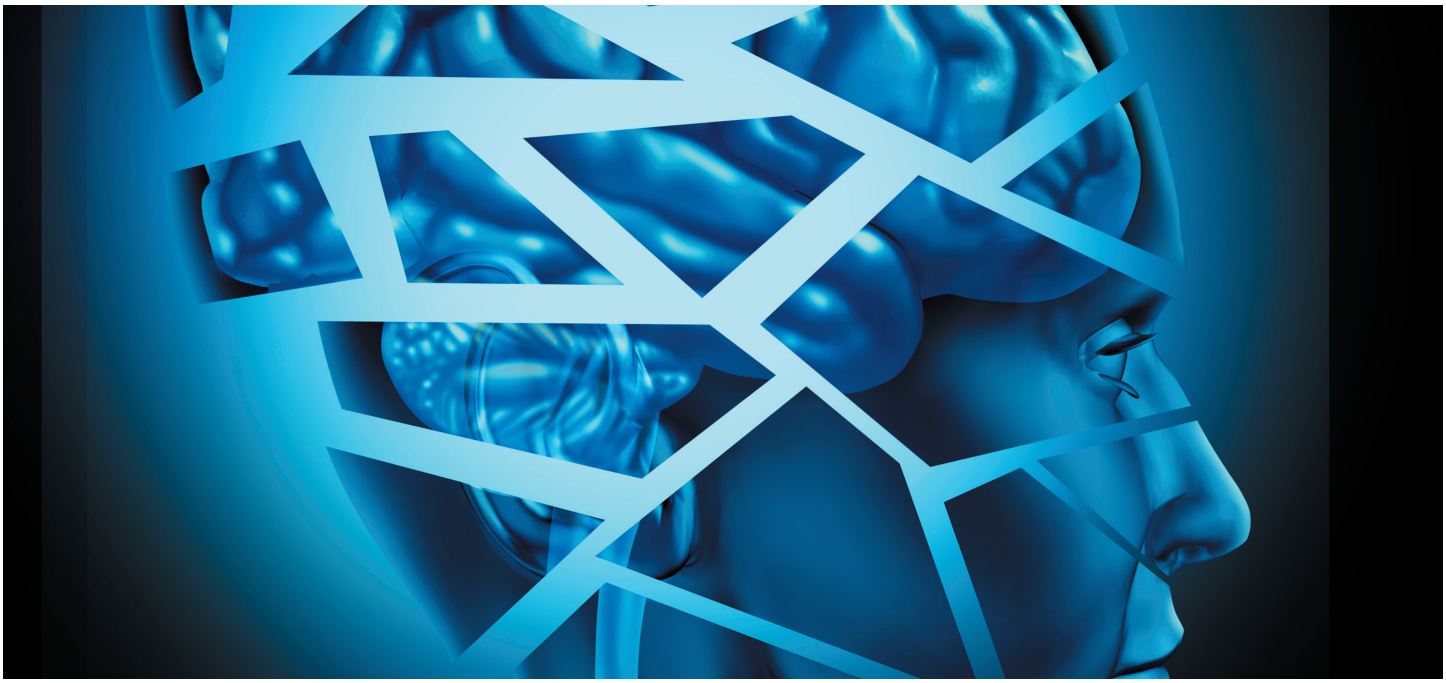
Articles are sourced from scientific journals, universities and publications that contribute to the ongoing research of brain injury.



The U.S. is Failing to Care for Traumatic Brain Injury Survivors, Experts Say

"We as physicians are frustrated that there are significant limitations to what we can do for our patients for an injury that has real-life, debilitating consequences"

Every year, nearly 5 million Americans are evaluated for traumatic brain injury in emergency departments across the country.

These injuries can happen in many different ways – from car crashes and military conflict to falls and everyday activities – and they're diagnosed in around 2% of all United States emergency department visits.

Awareness of the magnitude of TBIs has increased over the last several decades, particularly in sports and the military. But a group of experts from across the nation say the country's current system of care is often failing to meet the needs of the individuals, families and communities affected by traumatic brain injury.

"We as physicians are frustrated that there are significant limitations to what we can do for our patients for an injury that has real-life, debilitating consequences," said Frederick Korley, M.D., Ph.D., associate professor of emergency medicine at Michigan Medicine. "There are many important, structural changes that need to be made to provide

better care for patients who often go through a prolonged recovery process."

Korley is part of a select team of researchers who recently authored a report analyzing the health care system's response to TBI for the National Academies of Sciences, Engineering, and Medicine. The study, funded by the U.S. Department of Defense, found that the lack of a comprehensive framework for classification, care and research poses significant burdens for everyone involved – leading to needless death, squandered human potential and soaring costs. Their report contains numerous recommendations for improving TBI care and research.

TBI classification

When those near-5 million Americans arrive at the ER each year to be evaluated for brain injuries, they are placed into one of three categories: mild, moderate or severe.

It seems simple. The driver who is comatose after a devastating car crash would be considered severe, while the student who has a headache after slipping on black ice could be seen as mild. To Korley, who sees many of these so-called "mild" cases in the emergency department, the classification is inadequate – and, in some cases, insulting to patients.

"Some people who are considered 'mild' can't go to work; they have horrible headaches and memory problems that can result in losing a job or dropping out of school," he said. "Conversely, there are some people classified as 'severe' but actually do way better than we expect. Those cases don't all result in death or devastating disability."

This lack of distinction, the report notes, leads to suboptimal care across the spectrum of TBI and can include withdrawing life-sustaining treatment for patients who could have improved.

Instead of the shorthand, the researchers recommend using the full Glasgow Coma Scale score, a system that grades the severity of TBI on a scale from three to 15, in addition to results from brain CT scans and blood tests to classify patients. This approach provides a more accurate, nuanced assessment of the injury, Korley said.

"Let's say we have two cases of 'mild' TBI," he said. "One is a patient who has a concussion and experienced light sensitivity but felt fine not long after, and the other is someone who is awake but so out of it that they ask the same question repeatedly. The first would be a GCS 15, and the second would be a GCS 13. Calling both patients 'mild' is an oversimplification. Saying one is a GCS 15 TBI and the other is a GCS 13 TBI is more descriptive and will inform additional treatment plans."

Emergency physicians also rely heavily on neuroimaging through CT scans to find evidence of brain bleeding and determine if surgery is necessary. Recently, they have started using blood tests to justify neuroimaging and reduce the number of unnecessary scans. These blood tests can also help physicians better characterize the severity of the injury. The research team advocates for a classification system utilizing all three methods.

"This full range of analysis will make for a more accurate and sophisticated description of the injury that will inform individualized treatment and aid in predicting long-term outcomes more accurately," Korley said.

Delivery and continuity of care for patients with TBI

To many, the "traumatic brain injury" suggests an isolated event. A dramatic scene of a crash victim or wounded soldier receiving lifesaving medical intervention, possibly being cured.

This is a misleading view, Korley says. Think of TBI like COVID-19.

Many people who are hospitalized with the virus do not die, which could be seen as a

Think of TBI like COVID-19. Many people hospitalized with the virus do not die, which could be seen as a 'recovery.' But almost half of those people experience significant functional decline after they're discharged. And scores of people with 'mild infection' end up with lingering symptoms that can impact their lives.

'recovery.' But almost half of those people experience significant functional decline after they're discharged. And scores of people with 'mild infection' end up with lingering symptoms of long COVID that can impact their lives.

Like COVID-19, many of those 'recovering' from TBI experience a chronic phase of the injury. However, only 13 to 25% of patients with moderate-to-severe traumatic brain injury end up receiving interdisciplinary inpatient rehabilitation.

"There is the notion that once you leave the hospital after TBI, that's as good as it gets, but it's only the beginning of the battle," Korley said. "The acute phase is when you try to limit secondary brain injury. The chronic phase is a much longer healing process."

For an injury that researchers say is vastly undercounted, they note the United States has no mechanism for long-term TBI care. And for what is available, many survivors do not have, or cannot afford, access.

"Many people actually max out their benefits at that point [of inpatient rehab]," said one TBI patient quoted in the report. "Then when they are home, they have problems and don't have the insurance funds to help with those. To me, it's just criminal that so many victims of TBI are just forced by insurance companies into bed rest, which is just killing their chances of a good recovery."

Korley and the committee recommend creating a national framework for TBI care. They say it should build on the successes of regional trauma systems by establishing local and regional integrated care delivery systems across acute, rehabilitation and recovery phases of the injury. They also want health insurers, Medicare and Medicaid services to offer coverage for TBI care that aligns with clinical guidelines, ensuring equity in access and affordability.

"[Taking these steps] would require a level of continuity and acceptance of responsibility that American health care does not often achieve for chronic illnesses," researchers wrote.

Research and innovation

To date, there is no FDA-approved therapy that can treat damage from traumatic brain injury on its own. Several promising therapies have failed to promote recovery in large clinical trials.

Meanwhile, the committee says research on TBI is feeble compared to other important conditions, such as cancer or heart disease. They called for government organizations – the National Institutes of Health, the Department of Defense – and private sector funders to commit to a much larger investment in basic and clinical research to improve the health and well-being of TBI survivors.

Working with the Department of Defense, the Weil Institute for Critical Care Research and Innovation at University of Michigan hosts an annual Massey TBI Grand Challenge, which provides funding for early-stage, innovative and high-risk research to develop the next generation of diagnostics, devices and therapeutics for severe TBI. Researchers make 'Shark Tank'-style pitches to a panel of clinicians and commercialization experts for innovative ways to advance early care. Over six years, 39 teams have been funded with over $4 million awarded.

"This program provides a unique and vital mechanism to bring together diverse expertise from across U-M to propose and develop the almost-science fiction solutions and technologies that will be required to significantly impact the care of victims of TBI," said Kevin Ward, M.D., executive director of the Weil Institute and professor of emergency medicine and biomedical engineering at Michigan Medicine. "The program encourages collaboration across the medical, engineering, basic and computational sciences, and it is really helping us shorten the research and development cycle through strategic de-risking."

Without an entity taking charge to establish clear goals and conduct oversight, experts say, progress is unlikely.

"We want to drive more progress as we create a blueprint for clinicians, researchers and stakeholders who are committed to solving this problem," Korley said. "We are hoping that governmental leaders will pay attention and help redirect funding priorities. A lot of the recommendations we are proposing will take significant funding to implement. This is how our nation will start showing up for survivors of traumatic brain injury, their caregivers and communities." ■

Like COVID-19, many 'recovering' from TBI experience a chronic phase of the injury. However, only 13-25% of patients with moderate-to-severe TBI end up receiving interdisciplinary inpatient rehabilitation.

How Long Does It Really Take to Recover From Concussion?

A new study suggests that people with mild traumatic brain injuries may be more likely to have cognitive impairment, cognitive decline or both one year later, compared to people who were not injured. The research is published in the online issue of Neurology®, the medical journal of the American Academy of Neurology. People with poor cognitive outcomes were also more likely to have other symptoms like anxiety and lower satisfaction with life.

"Our results suggest that clinically meaningful poor cognitive outcomes, which we defined as cognitive impairment, cognitive decline or both, one year after a concussion may be more common than previously thought," said study author Raquel Gardner, MD, of the University of California San Francisco. "They also highlight the need to better understand the mechanisms underlying poor cognitive outcome, even after relatively mild brain injuries, to improve therapy for recovery."

The study looked at 656 people who had been admitted to trauma center emergency rooms with concussions and 156 healthy people without head injuries. Their average age was 40. Participants were given up to three neurological evaluations after their injury, at two weeks, six months and one year. Each of those evaluations provided five scores from three tests of recall, language skills and other cognitive domains.

Poor cognitive outcome was defined as satisfying the criteria for cognitive impairment, cognitive decline or both. Cognitive impairment was defined as lower-than-expected performance on at least two cognitive tests such as one memory test and one processing speed test. Cognitive decline was defined as clinically meaningful decline on at least two cognitive tests.

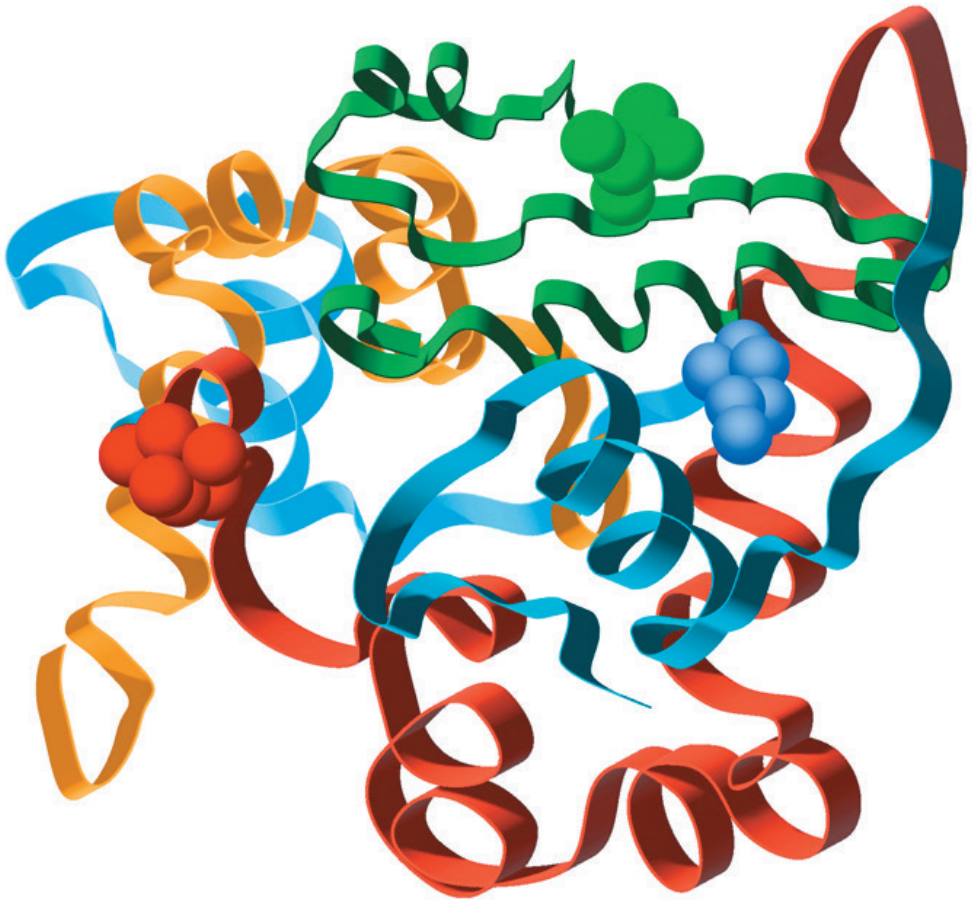
Researchers found that 86 out of 656 people with mild brain injuries, or 14%, had poor cognitive outcomes one year later. Of those, 10% had cognitive impairment only, 2% had cognitive decline only and 2% had both. That's compared to eight out of 156 people without concussions, or 5%, who had poor cognitive outcomes one year later. Of those healthy people, 3% had cognitive impairment, none had cognitive decline only, and 1% had both.

Researchers also found that people who had depression before their injury, had no health insurance, or had a high school education or less were more likely to have a poor cognitive outcome than those who were not depressed before the injury, or had insurance or had more than a high school education.

Researchers found that people who had good cognitive outcomes were more likely to have higher life satisfaction one year after their concussion. The life satisfaction test given to participants ranges in score from five to 35, with lower scores indicating lower life satisfaction. The people with good cognitive outcomes scored an average of 26 on the test, compared to people with poor cognitive outcomes, who scored an average of 21.

The study does not prove that people with concussions will have worse cognitive outcomes one year later, but it shows an association.

"Previous studies of people with moderate to severe brain injuries show that early, intensive rehabilitation can improve people's cognitive outcomes over time. More research is needed to find out the role of cognitive rehabilitation on people with more mild brain injuries who are also at risk for poor cognitive outcomes, and how to predict who falls into this risk category," Gardner said. ■



Brain Damage Higher Over Short Term in COVID-19 Patients Than in Alzheimer's Patients

The study found higher levels of seven markers of brain damage (neurodegeneration) in COVID-19 patients with neurological symptoms than those without them, and much higher levels in patients that died in the hospital than in those discharged and sent home.

Patients hospitalized for COVID-19 had higher levels over the short term of blood proteins known to rise with neurological damage than non-COVID-19 patients diagnosed with Alzheimer's disease, a new study finds.

Importantly, the current report, published online in Alzheimer's & Dementia: The Journal of the Alzheimer's Association, was conducted over two months early in the pandemic. Any determination of whether patients with COVID-19 are at increased risk for future Alzheimer's disease, or instead recover over time, must await the outcomes of long-term studies.

Led by researchers at NYU Grossman School of Medicine, the new study found higher levels of seven markers of brain damage (neurodegeneration) in COVID-19 patients with neurological symptoms than those without them, and much higher levels in patients that died in the hospital than in those discharged and sent home.

A second analysis found that a subset of the damage markers in

patients hospitalized with COVID-19, over the short term were significantly higher than in patients diagnosed with Alzheimer's disease, and in one case more than twice as high.

"Our findings suggest that patients hospitalized for COVID-19, and especially in those experiencing neurological symptoms during their acute infection, may have levels of brain injury markers that are as high as, or higher than, those seen in patients with Alzheimer's disease," says lead author Jennifer A. Frontera, MD, professor in the Department of Neurology at NYU Langone Health.

Study Structure/Details

The current study identified 251 patients that, although 71 years on age on average, had no record or symptoms of cognitive decline or dementia before being hospitalized for COVID-19. These patients were then divided into groups with and without neurological symptoms during their acute COVID-19 infection, when patients either recovered and were discharged, or died.

The research team also, where possible, compared markers levels in the COVID-19 group to patients in the NYU Alzheimer's Disease Research Center (ADRC) Clinical Core cohort, an ongoing, long-term study at NYU Langone Health. None of these 161 control patients (54 cognitively normal, 54 with mild cognitive impairment, and 53 diagnosed with Alzheimer's disease) had COVID-19. Brain injury was measured using single molecule array (SIMOA) technology, which can track the minute blood levels of neurodegeneration markers in picograms (one trillionth of a gram) per milliliter of blood (pg/ml), where older technologies could not.

Three of the study markers – ubiquitin carboxy-terminal hydrolase L1 (UCHL1), total tau, ptau181 – are known measures of the death or disabling of neurons, the cells that enable nerve pathways to carry messages. Levels of neurofilament light chain (NFL) increase with damage to axons, extensions of neurons. Glial fibrillary acidic protein (GFAP) is a measure of damage to glial cells, which support neurons. Amyloid Beta 40 and 42 are proteins are known to build up in patients Alzheimer's disease. Past study results argue that total tau and phosphorylated-tau-181 (p-tau) are also specific measures of Alzheimer's disease, but their role in the disease remains a matter of debate.

Blood markers in the COVID patient group were measured in blood serum (the liquid part of blood that has been made to clot), while those in the Alzheimer's study were measured in plasma (the liquid blood fraction that remains when clotting is prevented). For technical reasons, the difference meant that NFL, GFAP, and UCHL1 levels could be compared between the COVID-19 group and patients in the Alzheimer's study, but total tau, ptau181, Amyloid beta 40, and amyloid beta 42 could only be compared within the COVID-19 patient group (neuro symptoms or not; death or discharge).

Further, the main measure of neurological damage in COVID-19 patients was toxic metabolic encephalopathy, or TME, with symptoms from confusion to coma, and caused during severe infections by toxins generated as the immune system overreacts (sepsis), kidneys fail (uremia), and oxygen delivery is compromised (hypoxia). Specifically, the average percentage increase in levels of the seven markers for hospitalized patients with TME compared to those without neurological symptoms (figure 2 in the study) was 60.5 percent. For the same markers within the COVID-19 group, average percentage increase when comparing those successfully discharged home from the hospital to those who died in the hospital was 124 percent.

A secondary set of findings came from comparing NFL, GFAP, and UCHL1 levels in the serum of COVID-19 patients against levels of the same markers in the plasma of non-COVID Alzheimer's patients (figure 3). NFL was over the short term 179 percent higher (73.2 versus 26.2 pg/ml) in COVID-19 patients than in Alzheimer's patients. GFAP was 65 percent higher (443.5 versus 275.1 pg/ml) in COVID-19 patients than in the Alzheimer's patients, while UCHL1 was 13 percent higher (43 versus 38.1 pg/ml).

"Traumatic brain injury, which is also associated with increases in these biomarkers, does not mean that a patient will develop Alzheimer's or related dementia later on, but does increase the risk of it," says senior author Thomas M. Wisniewski, MD, the Gerald J. and Dorothy R. Friedman Professor in the Department of Neurology and director of the Center for Cognitive Neurology at NYU Langone. "Whether that kind of relationship exists in those who survive severe COVID-19 is a question we urgently need to answer with ongoing monitoring of these patients." ■

Injuries to Primary Visual Cortex Cause Long-Term Dysfunction of Neural Circuits

Even mild head injuries can mean serious consequences for brain function at its most basic level. Research published in Communications Biology shows that neuroplasticity, too, has its limits.

Injuries to the posterior occipital cortex are common in humans. Traumatic brain injury (TBI) can lead to long-term visual impairment (like loss of visual acuity). For example, estimates suggest that as many as 75% of current or former soldiers live with permanent visual dysfunction or cortical blindness. TBI is associated with mechanical brain damage and a wide range of neuronal abnormalities.

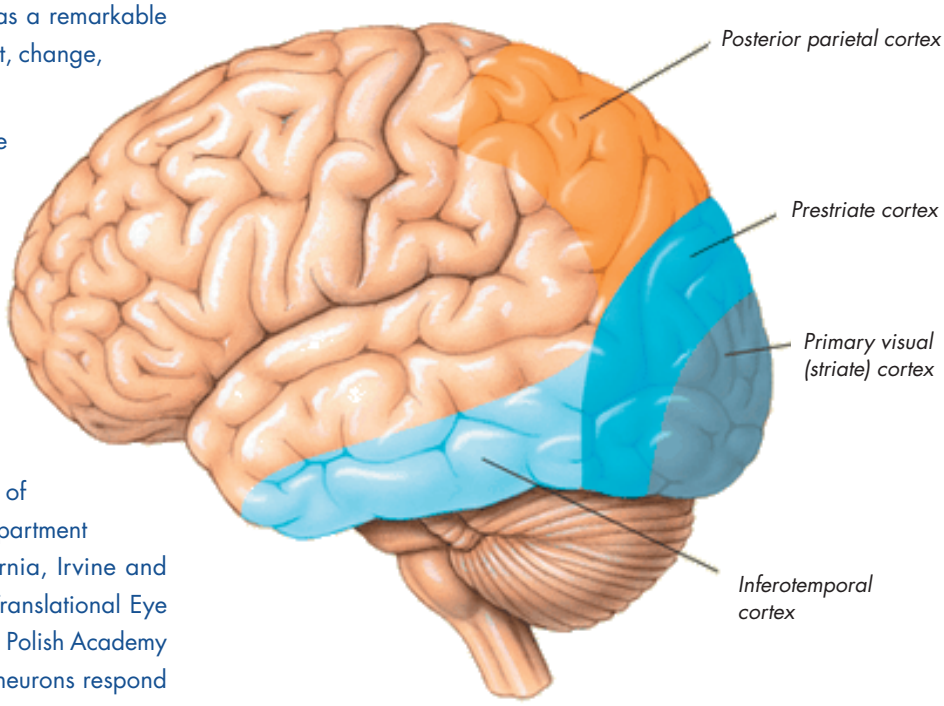
The human brain is characterized by surprising plasticity. Even when one part is injured, the functions of the damaged neurons can be taken over by other cells. This is because neural tissue has a remarkable ability to form new connections to reorganize, adapt, change, and self-repair the entire organ.

Such neuroplasticity is also characteristic of the sensory areas of the visual cortex. This region of the brain is the final component of the visual pathway, responsible for receiving and processing visual impressions. The primary visual cortex (V1) is reached by the nerve fibers of the optic radiation, which carry nerve impulses from the retinas of both eyes.

Until now, scientists knew little about the effects of TBI on long-term visual circuit function. A team of researchers led by John C. Frankowski from the Department of Anatomy & Neurobiology, University of California, Irvine and dr Andrzej Foik from the International Centre for Translational Eye Research (ICTER) at the Institute of Physical Chemistry, Polish Academy of Sciences, examined in vivo (in adult mice) how neurons respond to visual stimuli two weeks and three months after mild injury to the primary visual cortex (V1). V1 neurons normally show sensitivity to different features of a visual stimulus, such as color or direction of movement. The preprocessed data is transmitted to subsequent areas of the visual cortex. This study showed that although the primary visual cortex remained largely intact after the brain injury, there was a 35% reduction in the number of neurons. This loss largely affected inhibitory neurons rather than excitatory neurons, which, as their names indicate, inhibit or stimulate action in the target cells, respectively.

After TBI, less than half of the isolated neurons were sensitive to visual stimuli (32% at two weeks after injury; 49% at three months after the event), compared with 90% of V1 cells in the control group. There was as much as a threefold decrease in neuronal activity after the brain injury, and the cells themselves had worse spatial orientation. The overall results mean that even minor, superficial brain injuries cause long-term impairment in the way visual stimuli are perceived, persisting several months after the event.

A deeper understanding of the functional impairments in damaged visual cortex is important because it can provide a basis for developing circuit-level therapies for visual cortex damage. ■



Researchers Report Cognitive Effects of Aerobic Exercise on Persons with Significant Memory Loss caused by Traumatic Brain Injury

A pilot study by a team of rehabilitation researchers showed that 12 weeks of supervised moderate aerobic cycling may improve memory and processing speed in individuals with disabling cognitive deficits caused by traumatic brain injury. The study, the first of its kind in the brain injury population, was published online in Neurocase . The article, "The preliminary effects of moderate aerobic training on cognitive function in people with TBI and significant memory impairment: A proof-of-concept randomized controlled trial," was authored by Carly L.A. Wender, PhD, Brain M. Sandroff, PhD, Denise Krch, PhD, Glenn Wylie, DPhil, Nancy Chiaravalloti, PhD, and John DeLuca, PhD, of Kessler Foundation, and Christopher M. Cirnigliaro, PhD, and Jill Wecht, PhD, of the James J. Peters VA Medical Center, Bronx, New York.

Participants in the single-blind randomized control trial included 5 physically inactive individuals with a 10-year history of traumatic brain injury and significant memory impairment. They were randomized to 12-weeks of supervised moderate aerobic cycling exercise (intervention), or 12 weeks of stretching and toning exercise (control). All participants underwent neuropsychological tests of memory and processing speed and structural neuroimaging studies of the brain before and after their 12-weeks of exercise.

"Compared with controls, the exercise group demonstrated substantially greater improvements in auditory verbal learning and processing speed, and larger increases in volumes of their left hippocampus, left cerebellar cortex, and right cerebellar cortex," reported lead author Dr. Wender, postdoctoral fellow in the Center for Traumatic Brain Injury Research at Kessler Foundation. "We also found that large intervention effects favored the exercise group, which showed gains in processing speed and volume of the right thalamus."

Global cognitive impairments, as seen after traumatic brain injury, present major treatment challenges for clinicians, according to Brian Sandroff, PhD, senior research scientist in the Center for Neuropsychology and Neuroscience Research at Kessler Foundation. "Because of their effects on multiple cognitive domains, exercise interventions, which are low cost, noninvasive, and readily available, are an attractive option to explore in this population," he added.

Although this study is small and data are preliminary, this study is the first to look at cognitive function and morphological changes in the brain in response to exercise in people with traumatic brain injury related memory impairment. "Our results support the need to explore the relationships between exercise training, cognition, and functional and structural changes in the brain," Dr. Sandroff summarized, "which may establish the path toward optimal protocols for clinical implementation." ■

"Our results support the need to explore the relationships between exercise training, cognition, and functional and structural changes in the brain"

Small Study Finds Alzheimer's-Like Changes in Some COVID Patients' Brains

Phosphorylated tau in COVID patients could be a sign of early-stage Alzheimer's and also contribute to other neurological symptoms observed in COVID-19 patients.

A study from researchers at Columbia University Vagelos College of Physicians and Surgeons reports that the brains of a small sample of patients who died of COVID display some of the same molecular changes found in the brains of people with Alzheimer's disease.

The findings could help explain the memory problems reported by sufferers of "long COVID," though the researchers caution that the study is small – with data from only 10 patients – and needs to be replicated by others.

The study was published in Alzheimer's & Dementia: The Journal of the Alzheimer's Association.

Early reports of "brain fog" and persistent cardiac symptoms in COVID survivors prompted the Columbia researchers to investigate how certain molecules called ryanodine receptors were affected in this new disease.

Defective ryanodine receptors have been implicated in diverse pathogenic processes, ranging from heart and lung disease to the brain's response to stress and Alzheimer's disease, as reported in research led by Andrew Marks, MD, chair of the Department of Physiology & Cellular Biophysics at the Vagelos College of Physicians and Surgeons, who led the new study.

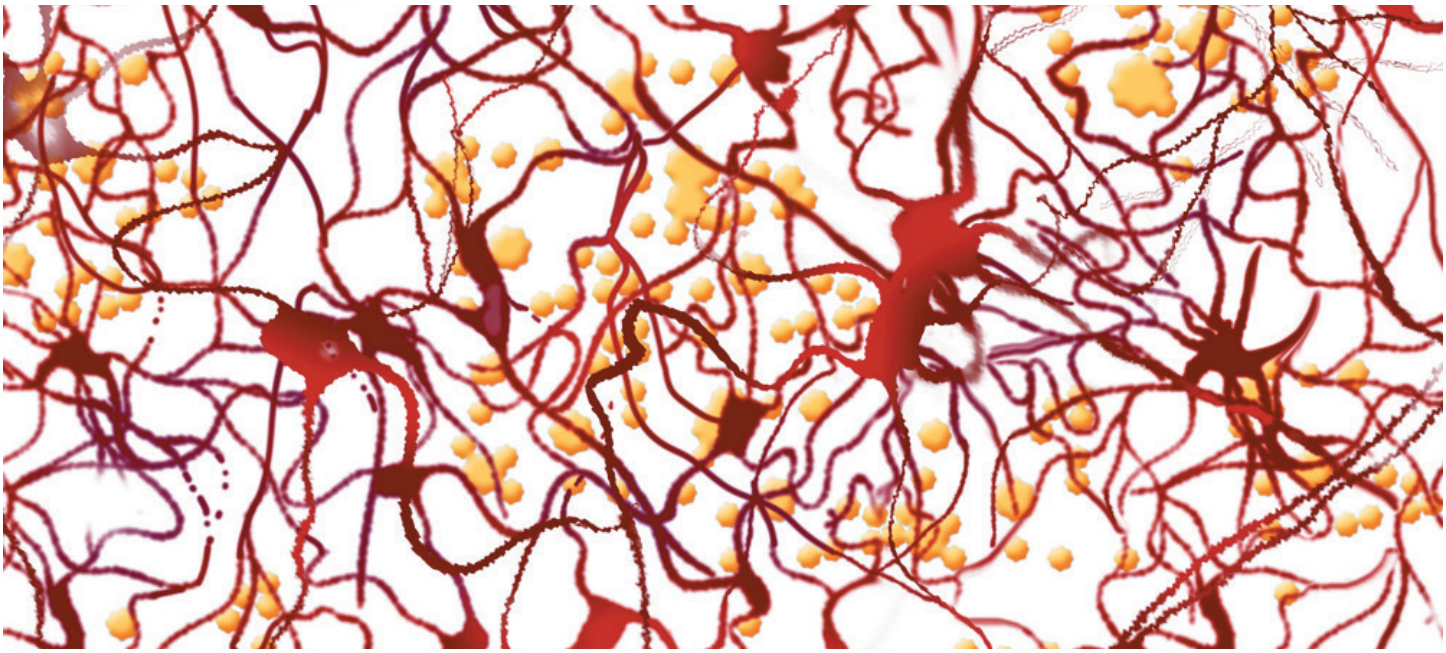
"When the COVID pandemic hit, like everybody else I was interested in being helpful and doing what we could do," says Marks. "What we found is really I think quite unexpected: Not only did we find defective ryanodine receptors in the hearts and lungs of deceased COVID patients, we also found them in their brains."

Molecular changes

Inside neurons, defective ryanodine receptors have previously been linked to an increase in phosphorylated tau, a well-known hallmark of Alzheimer's.

In the new study, the Columbia researchers found high levels of phosphorylated tau in the brains of the COVID patients in addition to defective ryanodine receptors.

Phosphorylated tau was found in areas where tau is typically located in Alzheimer's patients, as well as in areas where tau is not typically located in Alzheimer's patients. That suggests that phosphorylated tau in the COVID patients could be a sign of early-stage Alzheimer's and also contribute to other neu-



rological symptoms observed in COVID-19 patients.

Increased levels of phosphorylated tau in the brain are believed to be linked to memory problems in Alzheimer's and could be causing similar issues in people with long COVID, Marks says.

Based on the findings, together with additional changes found in the brain, the investigators theorize that the immune response characteristic of severe COVID causes inflammation in the brain, which in turn leads to dysfunctional ryanodine receptors and then increases in phosphorylated tau. No changes in the pathways that lead to the formation of amyloid beta -- another hallmark of Alzheimer's – were found.

Future directions

"One interpretation of these findings is that long COVID could be an atypical form of Alzheimer's and/or that patients who had severe COVID could be predisposed to developing Alzheimer's later in life," says Marks, "but much more research needs to be done before we can make more definitive conclusions."

If the memory and neurological problems of long COVID can be traced to defective ryanodine receptors, a drug under development by Marks may help. The drug is now in early clinical trials to treat a muscle disease caused by an inherited defect in the ryanodine receptor. The drug was able to fix the ryanodine defect when applied to the COVID patients' brain tissue.

"My greatest hope is that other laboratories will look into our findings, and if they are validated, generate interest in a clinical trial for long COVID," says Marks. ■

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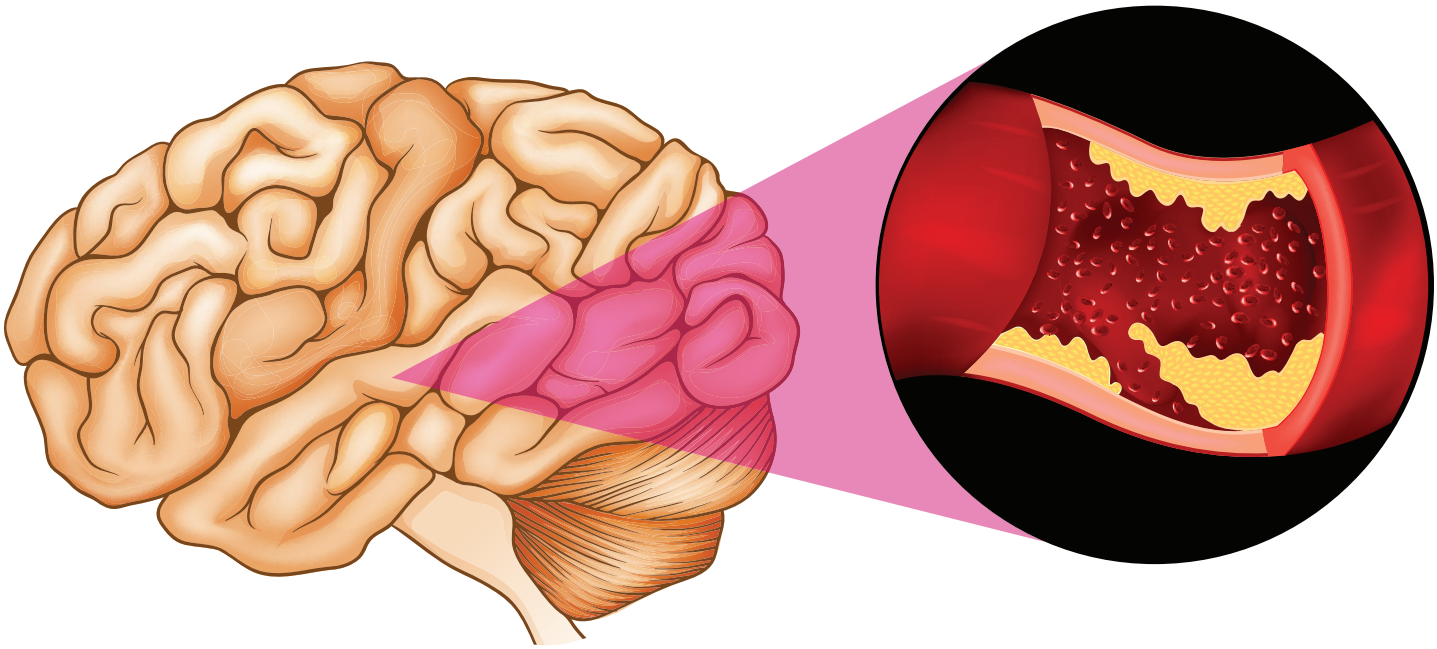

COVID-19-Associated Strokes Link to Higher Disability and Death Risk

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Among the many hard lessons from the COVID-19 pandemic is that SARS-CoV-2, the virus that causes COVID-19 infections, can affect every organ system in the body, including the brain.

Approximately one third of all patients with COVID-19 may develop neurological complications from infection, and many patients present to hospitals with acute ischemic stroke (AIS) or "brain attack," caused by the sudden blockage of blood flow to or within the brain.

As clinicians from Massachusetts General Hospital (MGH) and 29 other stroke centers across the U.S. and Canada now report, patients with COVID-19 who experience AIS appear to be at higher risk for severe disability and death compared with stroke patients treated in the pre-COVID era.

Adam A. Dmytriw, MD, MPH, MSc, an interventional neuroradiology & endovascular neurosurgery fellow at MGH and colleagues looked at records of 230 patients with AIS who were seen at the stroke centers during

the first wave of the pandemic, from mid-March through the end of August 2020.

As they reported in a freely available study in the Journal of Neurology, Neurosurgery & Psychiatry, a little more than half (51%) of all patients had poor outcomes, with 39.1% dying either in hospital or within 30 days of being discharged. In contrast, data from large clinical trials conducted before the pandemic show death rates of 27.6% among all patients with ischemic strokes, and 11.6% among patients with strokes caused by blockage of one or more large blood vessels that supply blood to much of the brain.

"There is an interaction that is still unknown between COVID respiratory disease and stroke, because the rate of poor outcomes or mortality is clearly greater than it would be in someone who had just an acute respiratory distress syndrome or COVID pneumonia, and also worse than someone who would have an equivalently large stroke in the pre-COVID era," Dmytriw says.

The still-growing North American Neurovascular COVID-19 (NAN-C) Consortium was founded by Dmytriw in collaboration with centers in New York and is supervised by Aman B. Patel, MD and Robert W. Regenhardt, MD, PhD at MGH.The hospitals participating in the study represent a broad spectrum of stroke centers with patients from a wide variety of socioeconomic backgrounds and varying access to care, Dmytriw notes.

"This study is something of a post-mortem of how the hardest hit areas responded to the first wave of the pandemic," he says. "Some of the initial reports we had came out of hospitals in more affluent areas such as central Manhattan where people with lower socioeconomic status were less likely to present. Even though Mass General is one such hospital, our goal was to create a consortium including hospitals in outer boroughs of New York, outside of the greater Boston area, within and around Detroit, as well as diverse centers from coast to coast."

"This study revealed how great the mortality was from COVID-associated stroke during the first wave, how high the rates of disability were for many patients, and that these mortality rates and disabilities were greater than those experienced in the first wave in other countries," he says.

The data suggest that patients from less affluent areas may have been at greater risk for serious complications such as stroke because of their inability to carry out protective measures such as social distancing or working at home, Dmytriw says. ■

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INSIDE VIEW

A Quarterly Magazine Dedicated to the Field of Acquired Brain Injury

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Centre for Neuro Skills is committed to helping those who have sustained a brain injury achieve the maximum possible quality of life and has served clients from around the world since 1980. CNS offers cost-effective, outcome-driven, community-based rehabilitation programs that focus on environmental validity, a normal rhythm of living, and obtaining the highest level of functioning for each client.

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