NYU Langone Health

Real-Time Innovation Sustains Quality Care in Neurology rough COVID-19 Response

Pediatric Patient with Puzzling Symptoms Leads Neurologists Toward Translational Discovery

With early reports indicating an association between COVID-19 and cerebrovascular disease, a team led by Shadi Yaghi, MD, associate professor in the Department of Neurology and research director of the Center for Stroke and Neurovascular Diseases, identi ed the critical, unmet need to document the mechanisms and outcomes of patients who have both a stroke and COVID-19.

STRATIF ING STROKE TO COMPARE CAUSE

Dr. Yaghi and team designed a retrospective, observational study examining ischemic stroke in patients with COVID-19 in order to elucidate the characteristics and causes of stroke with this speci c etiology. “We set out to answer whether the strokes we are seeing in patients with con rmed cases of COVID-19 are qualitatively di erent—in cause and course—from pre–COVID-19 cases we saw at the same time last year,” notes Dr. Yaghi.

e study, published in May 2020 in , examined all patients admitted for stroke across NYU Langone hospital locations in Manhattan, Brooklyn, and Long Island between March 15, 2020, and April 19, 2020. e primary inclusion criterion was hospital admission for stroke, con rmed by brain imaging. Patients were subsequently divided into three distinct groups: those with ischemic stroke and a con rmed COVID-19 diagnosis, contemporary control patients with stroke but without COVID-19, and patients with ischemic stroke and without COVID-19 from the identical time period in 2019.

Imaging and laboratory variables were evaluated to compare characteristics and subtypes of the stroke cases. ese variables included cardiac troponin level (upon admission), C-reactive protein (closest to the time of the stroke), erythrocyte sedimentation rate (closest to the time of the stroke), and D-dimer level (highest level and closest to the time of the stroke).

Among the initial ndings was a lower overall number of admissions for stroke during the 2020 COVID-19 pandemic trial period than during the corresponding period of 2019. “ is nding aligns with anecdotal reports of patients avoiding hospitals, in spite of stroke symptoms, for fear of contracting COVID-19,” says study co-author Jennifer A. Frontera, MD, professor in the Department of Neurology.

e actual number of imaging-con rmed ischemic strokes among patients with con rmed COVID-19 was also low: 32 of 3,556 patients studied, or 0.9 percent—though the researchers

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“Our results suggest that physicians need to be more aggressive in stabilizing body oxygen levels in patients with COVID-19 as a potentially key therapy for stopping, preventing, and/or possibly reversing neurological problems,” says study senior investigator Steven L. Galetta, MD.

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of autonomic involvement but none of those particular symptoms, so we recommended a treatment protocol to make her well enough to be discharged from the other hospital and seen in our clinic as soon as possible."

DIAGNOSIS B E CLUSION DEMANDS A NOVEL DIAGNOSTIC

To prepare for the patient's visit, Dr. Kaufmann and Dr. Palma examined the case symptom by symptom, ruling out conditions to reach a probable cause: an autoimmune response centered in speci c muscarinic receptors in the autonomic ganglia. Such receptors are abundant in the nervous system and critical to transmitting nerve signals to activate systems throughout the body. " e prevailing theory was that this patient's condition was caused by a problem with the nerve itself," says Dr. Kaufmann. "But we felt it was a problem with receptors in target organs, not nerves—the keyhole versus the key itself."

e patient's lack of central nervous system involvement pointed to an antibody binding to M3, one of ve muscarinic receptors. "Now that we had a suspected cause—an autoimmune process a ecting this M3 receptor—we needed to create experiments that could con rm the presence of antibodies and, in particular, characterize the interaction with the M3 receptor," notes Dr. Palma.

e related research of a longtime colleague led Dr. Palma to extend multidisciplinary collaboration beyond the walls of NYU Langone to partner with Salvador Sierra, MD, PhD, whose external laboratory was leading research focused on M3 receptors. Together, the physicians and researchers created tests to identify an antibody blocking activation of M3, as well as to rule out the other receptors' involvement. With the tests complete, the patient presented for examination and diagnostics.

"Our ndings supported our theory: Signi cantly increased levels of antibody were found to bind to M3," says Dr. Palma. e subsequent diagnosis of postganglionic cholinergic dysautonomia (PCD)—a rare disorder of unknown cause described in approximately 10 people—indicated continued therapy with the oral muscarinic receptor bethanechol. A repeat antibody assay found reduced levels of the antibody in the patient, whose symptoms had eased. " at second nding was consistent with our diagnosis, con rming that these antibodies had a relationship with the symptom severity in this patient," adds Dr. Palma.

RARE DISEASE OFFERS BROAD IMPLICATIONS

e path to diagnosis, published in August 2020 in , represents a translational medicine achievement with tremendous impact, both for this patient and beyond—and is exemplary of the kind of work enabled in part by 30 years of support from the Familial Dysautonomia Foundation. e patient is now feeling well, with the majority of her symptoms resolved. With her de nitive diagnosis—a known antibody blocking a receptor that unequivocally caused her disease—it's possible that her future treatment can be re ned. "Most autoimmune problems today are treated the same way, with medications that target the immune system," notes Dr. Kaufmann. "But as we further understand these disorders, we may be able to better target this patient's receptors with a more selective therapeutic."

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IMAGING COULD SHIFT THE CENTER OF ORIGIN IN LACUNAR STROKE

Ad hoc imaging postprocessing, executed by Eytan Raz, MD, PhD, assistant professor in the Department of Radiology, is informing a new understanding of the vascular origins of lacunar strokes—small strokes that occur deep within the brain's structures. Accounting for 15 to 20 percent of ischemic strokes, the subtype has long been thought to originate in thickening of the small

TREATMENT FOR POST STROKE FATIGUE COULD ENHANCE FUNCTIONAL OUTCOMES

In patients who experience profound strokes, both ischemic and hemorrhagic, sleepiness is a common and frequent barrier to positive rehabilitative outcomes. Disposition to acute rehabilitation requires patients to participate in a minimum of three hours of rehabilitation activities each day, a threshold reached by only 25.4 percent of patients. us, helping more patients—particularly younger patients poised for good outcomes—overcome lethargy and move into acute rehabilitation has become a priority for Jose L. Torres, MD, associate professor in the Department of Neurology. His new research suggests that the novel use of the stimulant drug moda nil can help patients overcome fatigue and reach the endurance benchmark needed to qualify for acute rehabilitation care, which is associated with better functional outcomes and reduced mortality as compared with discharge to other facilities.

New, Multisystem Insights Reveal Potential Treatment Pathways for Parkinson's Disease

UNCOVERING THE BRAIN CIRCUITR CHANGES IN PARKINSON'S DISEASE

Two National Institutes of Health (NIH)–funded studies led by Un Jung Kang, MD, the Founders Professor of Neurology, professor in the Department of Neuroscience and Physiology, and director of translational research in the Department of Neurology and Fresco Institute for Parkinson's and Movement Disorders, seek to reveal the dynamic betweeapeutic dopamine—the standard of care for patients with the condition—and the brain circuitry behind motor dysfunction.

In the rst study, Dr. Kang is mapping cell types in the brain's striatum to investigate how this circuitry in uences so-called motor learning, which may underlie the long-duration therapeutic response seen in dopamine-treated patients. "We're discovering that dopamine not only helps patients move better, but also contributes to sustained functional improvement," he says. "We're trying to understand what's behind this gradual buildup of bene t and how long it lasts."

Paradoxically, Dr. Kang and team are also investigating how brain compensation can interfere with dopamine's therapeutic e ects. When treatment begins, some patients' brain circuitry, having rewired itself to adapt to dopamine loss, leads to hypersensitive response. " ey go from movements that are too slow to uncontrolled movements that interfere with mobility for the opposite reason," notes Dr. Kang. " e rewired brain no longer knows what to do with the dopamine."

By understanding this e ect and the cellular-level changes in brain biochemistry, Dr. Kang hopes to ne-tune therapies by combining cell-selective, neuroanatomical, and biochemical approaches to target neurotransmitters beyond dopamine, with greater speci city than surgical therapies such as deep brain stimulation.

NON MOTOR S MPTOMS MA PREDICT DISEASE ONSET

Other research is targeting the e ects of Parkinson's disease beyond motor symptoms. Problems with sleep, blood pressure, constipation, and urination have become more prominent in a pati (omine1cy Tc T*or ion, and ur)c T*or ion, asymptey ( )]TJ 0 -18.6 (A)4.ivts oPor sa19.6 (1 (a)7 (t0 -18.6 m(omine1cadv T*ance-7 (ith (ep)3

Agarwal S, Conway J, Nguyen V, Dogra S, Krieger P, Zagzag D, Lewis A, Melmed K, Galetta S, Jain R. Serial imaging of virus-associated necrotizing disseminated acute leuko

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. , , was selected as the Daniel M. Jacobson Memorial Lecturer at the North American Neuro-Ophthalmology Society Annual Meeting in 2020 and will deliver the H. Houston Merritt Lecture during the Presidential Plenary Session of the American Academy of Neurology 2021 meeting.

B . ,' , received the Irma T. Hirschl Career Scientist Award and delivered a keynote lecture at the 26th Annual Meeting of the Organization for Human Brain Mapping (OHBM). Dr. He was also appointed a consulting editor for the *Journal of Cognitive Neuroscience*.

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