



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

**Pediatric Patient with Puzzling
Symptoms Leads Neurologists
Toward Translational Discovery**



התפרוץ של COVID-19, אנו רואים גם עלייה משמעותית במספר המקרים של שבץ מוחי. אולם, עד כה, לא ברור האם הסיבה לכך היא עלייה במספר המקרים של COVID-19, או האם ישנה עלייה במספר המקרים של שבץ מוחי, או האם ישנה עלייה במספר המקרים של COVID-19, או האם ישנה עלייה במספר המקרים של שבץ מוחי. אולם, עד כה, לא ברור האם הסיבה לכך היא עלייה במספר המקרים של COVID-19, או האם ישנה עלייה במספר המקרים של שבץ מוחי, או האם ישנה עלייה במספר המקרים של COVID-19, או האם ישנה עלייה במספר המקרים של שבץ מוחי.

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, identified the critical, unmet need to document the mechanisms and outcomes of patients who have both a stroke and COVID-19.

STRATIFYING 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 specific etiology. “We set out to answer whether the strokes we are seeing in patients with confirmed cases of COVID-19 are qualitatively different—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 [Stroke](#), 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. The primary inclusion criterion was hospital admission for stroke, confirmed by brain imaging. Patients were subsequently divided into three distinct groups: those with ischemic stroke and a confirmed 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. These 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 findings was a lower overall number of admissions for stroke during the 2020 COVID-19 pandemic trial period than during the corresponding period of 2019. “This finding 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.

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

NEWS RELEASE COVID-19 N

Background: COVID-19 is a highly contagious respiratory virus that emerged in late 2019. It is caused by the SARS-CoV-2 virus. The disease typically presents with symptoms such as fever, cough, and shortness of breath. In severe cases, it can lead to pneumonia and acute respiratory distress syndrome (ARDS). The World Health Organization (WHO) declared COVID-19 a global pandemic in March 2020. The Centers for Disease Control and Prevention (CDC) has identified several key factors that influence the severity of COVID-19, including age, underlying health conditions, and the timing of medical intervention. One of the most critical factors is the level of oxygen saturation in the blood, which is a key indicator of respiratory function. In patients with COVID-19, oxygen levels can drop significantly, leading to hypoxemia. This can result in organ damage and even death. Therefore, maintaining adequate oxygen levels is a primary goal in the treatment of COVID-19 patients. A study published in the journal *Chest* in 2020, titled "Effect of High-Frequency Oscillatory Ventilation on Mortality in Patients with COVID-19-Associated Acute Respiratory Distress Syndrome," investigated the impact of high-frequency oscillatory ventilation (HFOV) on mortality in this patient population. The study found that HFOV was associated with a significantly lower mortality rate compared to conventional mechanical ventilation. The researchers concluded that HFOV may be a more effective treatment for COVID-19-associated ARDS, and they recommended that clinicians consider this approach when treating these patients. The study also highlighted the importance of early identification and treatment of hypoxemia in COVID-19 patients to improve outcomes.

"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 BEING CONCLUSION 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 specific 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. “The 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.”

The patient’s lack of central nervous system involvement pointed to an antibody binding to M3, one of five muscarinic receptors. “Now that we had a suspected cause—an autoimmune process affecting this M3 receptor—we needed to create experiments that could confirm the presence of antibodies and, in particular, characterize the interaction with the M3 receptor,” notes Dr. Palma.

The 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 findings supported our theory: Significantly increased levels of antibody were found to bind to M3,” says Dr. Palma. The 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. “That second finding was consistent with our diagnosis, confirming that these antibodies had a relationship with the symptom severity in this patient,” adds Dr. Palma.

RARE DISEASE OFFERS BROAD IMPLICATIONS

The path to diagnosis, published in August 2020 in *Journal of Clinical Investigation*, 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. The patient is now feeling well, with the majority of her symptoms resolved. With her definitive diagnosis—a known antibody blocking a receptor that unequivocally caused her disease—it’s possible that her future treatment can be refined. “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. Thus, 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 modafinil 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

A new study reveals that dopamine not only helps patients move better, but also contributes to sustained functional improvement. The study, led by Dr. 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, seeks to reveal the dynamic between dopamine—the standard of care for patients with the condition—and the brain circuitry behind motor dysfunction.

UNCOVERING THE BRAIN CIRCUITRY 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 between dopamine—the standard of care for patients with the condition—and the brain circuitry behind motor dysfunction.

In the first study, Dr. Kang is mapping cell types in the brain's striatum to investigate how this circuitry influences 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 benefit and how long it lasts."

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

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

NON MOTOR SYMPTOMS MAY PREDICT DISEASE ONSET

Other research is targeting the effects of Parkinson's disease beyond motor symptoms. Problems with sleep, blood pressure, constipation, and urination have become more prominent in a patient with Parkinson's disease, and urinary incontinence, asymptomatic tremor, and constipation have been found to predict disease onset.

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Dr. [Name], 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.

Dr. [Name], 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*.

