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FEBRUARY 01, 2021

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Contents

- Feature. COVID Peripheral Nerve Damage & Diaphragm Muscle Dysfunction: Key Learnings
- Buzzworthy. Perspectives on Creating a Novel Residency Track
- Science IRL. Re-igniting the connection between brain and spinal cord
- Influencer. From high-flying gymnast to sports science scholar

Feature. COVID Peripheral Nerve Damage & Diaphragm Muscle Dysfunction: What We've Learned



Colin Franz, MD, PhD ('17 Residency)
Attending Physician and Director, Electrodiagnostic Laboratory, Shirley Ryan AbilityLab
Assistant Professor, Northwestern University

In March 2020, Shirley Ryan AbilityLab neuromuscular researcher Colin Franz, MD, PhD, began noticing the significant debilitation of patients who had survived severe cases of COVID-19. This awareness motivated him to shift the focus of his research.

Six months later, Dr. Franz and his team published a paper in the *British Journal of Anaesthesia* that identified permanent nerve damage in patients with COVID-19 who had been on ventilators and placed in a prone position. This discovery has led to improvements in patient care.

How does an expert in nerves — who, by his own admission, "doesn't know about virology or immunology" — contribute to the fight against COVID-19? What vital role do physiatrists play in the care of COVID-19 patients? How did Shirley Ryan AbilityLab's unique medical residency research track set up Dr. Franz for success?

Read the conversation with Dr. Franz.

What was the catalyst for your research?

I'm an outpatient physician and scientist, and I run the Electrodiagnostic Lab at Shirley Ryan AbilityLab. In the early days of COVID-19, when we were all in the "fog of war," all outpatient services largely came to a halt, and I was originally person left running my research lab and performing EMG tests. Dr. Rydberg and Dr. Soriano, who were working on our COVID Care Unit, told me about a patient who they thought had a nerve injury, and asked me to do an EMG. Within a few days, there was a second patient with nerve injury. Then, a third. For a few months, these tests and consultations on COVID patients with neuromuscular complications consumed my clinical work.

In the process, I found that approximately 15% of the most severely ill COVID patients — those who were placed in the prone position in the ICU — have permanent nerve damage. I had some patients who had up to nine distinct neuromuscular diagnoses by the end of a test. Injuries to arms and legs outside of the central nervous system are devastating and underappreciated, as nerve regeneration is so slow and inefficient in the peripheral nervous system. Because of the nature of the nerve and muscle damage, these survivors of severe COVID will be the ultimate long-haulers and will continue to need extensive rehabilitation for months, if not years.

I wasn't the first physiatrist on campus to be asked to step up to the challenge of COVID-19, but I found a role in which I was uniquely suited to make a contribution. I'm grateful for the opportunity to help these patients.

How can physiatrists identify this COVID-related nerve damage? What are the warning signs?

The biggest warning sign in recognizing acquired nerve injuries in COVID-19 patients is asymmetrical weakness that is way out of proportion with the opposite side of the body. Of course, in rehabilitation medicine, we're used to symmetrical weakness patterns from myopathy and neuropathy after critical illness. The situation with COVID patients is different, however; when we frequently see asymmetry — like wrists, ankles or shoulders paralyzed on just one side of the body — it's a clue that we need to investigate more.

A second hidden neuromuscular complication involves the diaphragm. At the recent AAPM&R meeting, I presented unpublished data in which we used ultrasound and found an incredibly surprising amount of diaphragm muscle weakness in the vast majority — 80%! — of COVID patients who have survived critical care. This weakness is in addition to the shortness of breath from pneumonia-related lung damage caused by COVID infection. However, the substantial weakness in the diaphragm muscles is expected to make recovery slower as it represents an acquired neuromuscular respiratory disease.

Another telltale sign with these patients is when shortness of breath affects sleep — they're not getting good oxygenation, and they can't lie flat. As a result, they wake up throughout the night, or they have a headache in the morning. You can even see metabolic disturbances on basic laboratory tests, such as an elevated bicarbonate level related to hypercapnia. If anyone comes into rehabilitation after COVID, I'd suggest screening through a neuromuscular diaphragm ultrasound examination.

Most physicians trained in internal medicine are not going to pick up on this kind of shortness of breath, so it's up to physiatrists — those of us who think about nerves and muscles — to be on the lookout for these issues and be prepared to address them creatively.

Is there anything about COVID patients as a group that is different from other PM&R patients?

They never seem to complain! Severe COVID-19 survivors have been through such a terrible illness, and they have every reason to complain, but they don't. I'd ask patients what their issues were, and they would say, "You know, Doc, I'm doing pretty well, actually" — even when they couldn't lift an arm or move a leg. As a result, nerve injuries are no doubt overlooked and underreported. It's up to us to identify and address these issues.

What's next with your work with COVID-19 patients?

COVID-19 has presented us with an opportunity to accelerate some of the research on nerve damage that we were already leading. In terms of diagnostics, we've been really interested in identifying better ways to characterize and locate nerve problems. Our ability to do so has been improving through use of better techniques, including advanced imaging options such as MRIs and high-resolution neuromuscular ultrasound. The benefit of our field is that we can analyze living, breathing, rehabbing COVID survivors — and learn much in the process.

One major problem to solve relates to positioning. For prevention and quality improvement, prone positioning for respiratory symptoms is potentially life-saving. However, sustaining that position over time is associated with significant nerve damage. To address this central issue, we've developed a pressure map of hot spots for nerve sensitivity and suggested modifications to the ICU protocol. We're also developing sensors for new applications to identify nerves under distress *before* they get damaged.

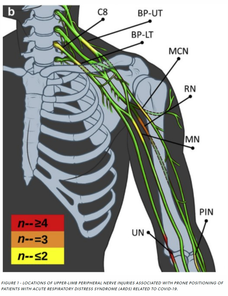


FIGURE 1 - LOCATIONS OF UPPER-LIMB PERIPHERAL NERVE INJURIES ASSOCIATED WITH PRONE POSITIONING OF PATIENTS WITH ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS) RELATED TO COVID-19.

Most COVID patients won't need surgery, but their nerves do need to heal. On the therapeutics front, we are ready to roll out a precise, non-invasive, low-frequency stimulation to the nerve that is just proximal to point of injury. We're developing a protocol out of our bench work to guide us in understanding the best dosage so that we can optimize it accordingly and make the data available.

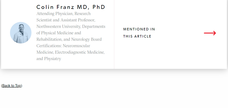
With so many people infected with COVID-19, it's a race to get our insights out there and to help as many patients as possible. Every article we've published is available on open access. I also welcome connections and discourse through Twitter.

You were Shirley Ryan AbilityLab's first resident in the research track — what was that experience like and how was it unique?

Shirley Ryan AbilityLab initially committed time and resources to develop this first-of-its kind program more than a decade ago. When I first met with [Chief Medical Officer] Dr. Jim Sliwa before I started my residency, he laid out the research track for me. It was exciting to give my input to make the program even better, because no one had done it before. In time, a lot of doors opened up for me to do high-powered science. Now, the program's offered to every single resident who sets foot in the building. Every time I interview applicants, they ask me about it.

What impact did the research track have in shaping your approach to practice and your COVID research?

My research looked at using activity to augment or enhance nerve repair and regeneration. Looking back, I benefited from the unique insights gleaned from working with patients, identifying problems and finding ways my research could help address those problems — it was a kind of reverse translation. By having better insights, I was able to ask even better questions and be more creative in my thinking and approach.



(Back to Top)

Buzzworthy. Perspectives on Creating a Novel Residency Track

A decade ago, Shirley Ryan AbilityLab launched a 5-year research residency track. Learn about its structure, and capture key takeaways on building a program from the ground up.



(Back to Top)

Science IRL. Re-igniting the Connection Between Brain and Spinal Cord

Monica A. Perez, PT, PhD, Scientific Chair of the Arms + Hands Lab at Shirley Ryan AbilityLab, has developed a non-invasive brain and peripheral nerve stimulation treatment that, paired with physical therapy, has been shown to mend the broken connection between the brain and spinal cord for at least six months.

Neurostimulation Improves and Preserves Rehabilitation Gains

What's the big deal? Rehabilitation of patients with spinal cord injury (SCI) can be accomplished by combining neural stimulation with physical therapy. Several studies have found that rehabilitation can be augmented by neurostimulation, but previous studies have used protocols with limited or short-lasting results. The first randomized placebo-controlled clinical trial was recently completed by Dr. Perez and her team, and demonstrated that a novel neurostimulation protocol (referred to as paired corticospinal-motoneuronal plasticity or PCMS), combined with standard physical therapy, maximized clinical outcomes in SCI patients, with effects lasting for six months!

What did they find? Patients with chronic incomplete SCI at different levels (cervical, thoracic or lumbar) were recruited. They were randomized into two groups: a group that received 10 sessions of physical therapy for 45 minutes after 30 minutes of targeted PCMS (n=13), or a group that received 10 sessions of physical therapy for 45 minutes after sham-PCMS (n=12). An additional experiment tested the effect of PCMS without physical therapy (n=13) in a similar cohort. The targeted neurostimulation protocol was customized to include patients with different levels of injury. Corticospinal excitability and the magnitude of maximal voluntary contractions in targeted muscles increased by 40%–50% after PCMS with or without physical therapy, but not after sham-PCMS. Improvements in the time to complete subcomponents of the Graded and Redefined Assessment of Strength, Sensibility and Prehension (GRASSP) and the 10-meter walk test were preserved for six months only in the group that received physical therapy plus PCMS (Figure 1). This study is one of the very few to show that the functional gains due to neurostimulation actually last up to six months.

How does this affect how I treat patients? The findings demonstrate that exercise-mediated rehabilitation recovery in humans with different levels of SCI can be enhanced and preserved by using targeted non-invasive stimulation of spinal synapses.

Reference: Jo HJ, Perez MA. (2020). Corticospinal-motor neuronal plasticity promotes exercise-mediated recovery in humans with spinal cord injury. BRAIN. 143: 1368–1382.

(Back to Top)

Influencer. From High-flying Gymnast to Sports Science Scholar



Ellen Casey, MD, FACSM
('09 Residency, '10 Sports Medicine Fellowship)
Associate Attending Physiatrist, Hospital for Special Surgery
Associate Professor, Weill Cornell Medical College
Team Physician, USA Gymnastics Women's National Team

Dr. Casey discusses her research and the impact of sex, gender and hormones on musculoskeletal injuries.

How do you describe your practice?
I have an academic practice at the Hospital for Special Surgery in New York with clinical, teaching and research duties. My clinical practice is a 50/50 split of sports and spine medicine. My sports practice tends to support gymnasts, dancers and endurance athletes. With spine, I see everyone from a young athlete with a stress fracture in her back to patients in their 90s with stenosis.

What has been your research focus?
When I was doing my physiatry residency, I learned that female athletes are at two to eight times greater risk of ACL injury compared with male athletes. I found this disparity to be unacceptable, and it piqued my interest in understanding why. One of the many reasons for this sex disparity is hormonal differences, so I began to research the modulatory role of sex hormones in ACL injury.

We must not only understand how the risk of ACL injury changes across the menstrual cycle, we must also understand how we can mitigate that risk. A coach isn't going to bench a basketball player because she's ovulating and is at increased risk to tear a ligament. However, there are other possible protections we can explore.

Recently, we did a survey of more than 1,000 female college athletes, and found that 66% are taking hormonal contraceptives — for reasons other than ligament health, obviously. The next step is to understand whether one contraceptive pill is better than others — there is some preliminary data indicating that the type of progesterone and quantity of estrogen in a contraceptive pill likely affect ligaments differently. Just think about it: If you are taking hormonal oral contraceptives, and one type prevents ACL injury better than another, why not take that one? This insight allows us to take a previously considered non-modifiable risk factor and make it modifiable with something that people are already doing.

What is your background in gymnastics, and how did it lead you to physiatry?
Starting at age nine, and continuing through high school, I competed in gymnastics and was fortunate to receive a full gymnastics scholarship to Penn State, where I competed for the university. At that point, I started getting interested in biomechanics, because gymnastics is like a living example of biomechanics. I was drawn to medicine because I wanted to understand how to identify risk factors for gymnastics-related injury and how to intervene to prevent injury.



DR. ELLEN CASEY, PICTURED SECOND FROM RIGHT AT THE 2019 GYMNASTICS WORLD CHAMPIONSHIP IN GERMANY.

Now, in my role with USA Gymnastics, we're starting to look at ways to monitor and follow workload in terms of training, intensity and duration. Gymnastics is well behind other sports in the utilization of sports science. Every sport is different, so the variables will be different, but I would love for the sport to start adopting more of an evidence-based and science-based approach. I've been working with colleagues to develop some reasonable workload trackers, and we hope to collect injury and epidemiology data. We want to overlay that data with workload data to understand some of the risk factors for injury, and then create strategies for prevention.

Recent Publications

- Menstrual Irregularity, Hormonal Contraceptive Use, and Bone Stress Injuries in Collegiate Female Athletes in the United States
- Identification of Risk Factors for Injury in Women's Collegiate Gymnastics With the Gymnastics Functional Measurement Tool
- Musculoskeletal Consequences of COVID-19

Dr. Casey works in New York City, but lives in Philadelphia with her husband, 9-year-old son and almost-7-year-old daughter.

(Back to Top)