TEXAS NEUROLOGICAL SOCIETY SUMMER 2021

Broca's Area

The Voice of Texas Neurology

President's Message

14 months ago, I could not have imagined that I would write a chapter for a neurology publication with the above words; these words are represented in size by how frequently they appeared in the chapter. Teleneurology, telemedicine, virtual and hybrid were the most commonly used words. We have all been locked in a Groundhog Day-like situation of isolation, PPE, Zoom meetings, virtual professional meetings, telemedicine and teleneurology. Our Texas Neurological Society Winter Conference was a very successful virtual meeting. So, Texas Neurologists have proven to be adaptable, resilient, and patient advocates in the most significant pandemic of our lifetime.

As of May 5th, 38% of Texans have received at least one dose of a COVID-19 vaccination, and the positivity rate in most communities is down below 5%. Hospitalizations are down, but still significant. Unfortunately, people are still dying from COVID-19. Some of us feel "Vacciliberated", yet the world is not breathing a sigh of relief. Do we dare go out to a restaurant? Do we dare to consider traveling again? Do we get to live a different life from the past 14 months? Do we have a virtual summer meeting or an in-person summer meeting for the Texas Neurological Society?

Many societies are planning in-person meetings in the fall of this year. Some are planning hybrid meetings with in-person and virtual or online options. Can we be the tip of the spear for the summer meeting?

I don't know about you, but I do miss seeing you all, in person, and not on a computer screen. We are planning to convene the summer meeting in Austin on July 23 and 24. The meeting will be in-person at the Omni Barton Creek Austin, and it will have an online option – thus a hybrid meeting. I believe that we may be the first of the Texas medical societies to attempt a hybrid meeting. Of course, we will use CDC guidelines and maintain safety protocols so that we are not a culprit in the spread of SARS-CoV-2. I am looking forward to getting out of my Groundhog Day burrow; I hope that you are too! I will see you in Austin – in-person or virtually.

Gary D. Clark, MD

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TNS Brocas is digital and interactive

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Editor's Notes

Randolph W. Evans, MD

I thank our officers and other contributors for their excellent submissions to this issue. We look forward to seeing you (hopefully in person but we'll have a hybrid meeting) at the TNS Summer Conference at the Omni Barton Creek July 23-24 in Austin. Dr. Olga Waln, program director, and the education committee have planned an excellent program.

FOR WHOM THE BELL TOLLS. ERNEST HEMINGWAY AND CHRONIC TRAUMATIC ENCEPHALOPATHY

Some of you may have watched the recent 3 part PBS series, "Hemingway. The Man. The Myth. The Writer Revealed," by Ken Burns and Lynn Novick. If you haven't, I highly recommend it if you're interested in Hemingway, the first 60 years of the 20th century, or TBI (available free at https://www.pbs.org/kenburns/hemingway/#video).

Hemingway (1899-1961) was one of the great American writers of the 20th century, as famous as Mark Twain, and a winner of the Pulitzer Prize in 1953 and the Nobel Prize in 1954. Hemingway, the man and the myth, regularly intermingled as his life was too unique to make up and became the source for his fiction. He was the real world's most interesting man whose motto could also have been, "Stay thirsty, my friends." (Interestingly, when Dos Equis was casting, they wanted a Hemingway kind of guy and found Jonathan Goldsmith).

Tragically, in his final years, Hemingway was markedly impaired with paranoid delusions, irrationally violent towards his wife, cognitively impaired, and had lost his ability to write. There has long been speculation about the possible causes including his alcoholism (he described life without alcohol as driving a race car without motor oil), diabetes, hypertension, and long-standing depression present since childhood.

Another consideration is the cumulative effect of multiple concussions and possible chronic traumatic encephalopathy as detailed by psychiatrist, Andrew Farah

Perhaps Hemingway foretold his CTE in one of his early short stories, "The Battler," published in 1925.

A man goes into the woods and meets a disfigured prizefighter who was insightful but prone to fits of paranoia and violence.

"You're all right," says the visitor after they've chatted a while.

"No, I'm not. I'm crazy," the fighter says. "Listen, you ever been crazy?"

"No. How does it get you?"

"I don't know. When you got it you don't know about it."

In 1928, Martland described "a peculiar condition" among prize fighters, "punch drunk." Millspaugh introduced the term "dementia pugilistica" in 1937.

Hemingway may have had concussions playing football in high school and boxing. He once said in an interview, "My writing is nothing, my boxing is everything."

While in Paris, Hemingway invited heavyweight titlist, Jack Dempsey, to spar who declined. "He was about twenty-five or so and in good shape, and I was getting so I could read people, or anyway men, pretty well. I had this sense that Hemingway, who really thought he could box, would come out of the corner like a madman. To stop him, I would have to hurt him badly. I didn't want to do that to Hemingway. That's why I never sparred with him."

In Paris in 1929, Hemingway sparred with Canadian writer Callahan with F. Scott Fitzgerald as the timekeeper. In the second round, Fitzgerald accidently extended the time to a minute allowing Callaghan to knock out Hemingway. There's even a 2 minute video depiction of the bout with commentary from Callaghan on YouTube.

Hemingway later had a boxing ring at his Key West Home and employed a trainer. In Bimini in 1935, he offered $250 to anyone who could knock him out in 3 rounds. Four people failed.

Hemingway had a wild and crazy life sustaining numerous well documented concussions, many occurring in memorable contexts.

1 In World War I, while serving with the Red Cross (figure 1) on canteen duty in northern Veneto, Italy in 1918, a five-gallon Austrian mortar exploded throwing him several feet, knocking him unconscious and giving him 28 shrapnel wounds in the legs. Two men near him were killed. As he was lifting another man to safety, he was struck in the right knee with machine gun fire.

Blast wave trauma number one.

Hemingway described this event in his 1929, "A Farewell to Arms," through his protagonist, Frederick Henry:

> "I ate the end of my piece of cheese and took a swallow of wine. Through the other noise I heard a cough, then came the chuh-chuhchuh-chuh. Then there was a flash, as when a blast-furnace door is swung open, and a roar that started white and went red and on and on in a rushing wind. I tried to breathe but my breath would not come and I felt myself rush bodily out of myself and out and out and out and all

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Editor's Notes (cont.)

Figure 1. Hemingway in Milan, June, 1918

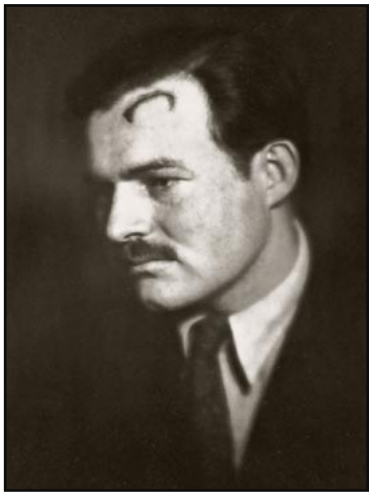

Figure 2. Hemingway after forehead laceration sustained in Paris, 1928

> the time bodily in the wind. I went out swiftly, all of myself, and I knew I was dead and that it had all been a mistake to think you just died. Then I floated, and instead of going on I felt myself slide back. I breathed and I was back. The ground was torn up and in front of my head there was a splintered beam of wood. In the jolt of my head I heard somebody crying.

I sat up straight and as I did so something inside my head moved like the weights on a doll's eyes and it hit me inside in back of my eyeballs. I knew that I was hit..."

2 In 1928, he was drinking all night with Archibald MacLeish. He came home and went into the bathroom at 2 am. Upon flushing the toilet, he pulled the skylight cord rather than the toilet chain and the skylight fell on his head. He had a concussion and sustained a forehead laceration and permanent scar (figure 2).

3 During World War II, on May 26, 1944, after partying with Robert Capa (born Endre Friedman; perhaps the greatest combat photographer) in London, the designated driver was "no drunker than Hemingway." What could go wrong during the black out of the Blitz? They ran into a water tower. Hemingway went into the windshield and had 57 stiches in the forehead. He reported double vision, memory problems, slowed thought, and headaches "that used to come in flashes like battery fire. There was a permanent one all the time. I nicknamed it the MLR2 (main line of resistance) and just accepted that I had it."[3] He was in the hospital for a few days.

As a war correspondent for Collier's magazine, he sailed for Normandy on June 5, 1944 with U.S. troops on a transport ship reaching the shallow waters of Omaha Beach in the seventh wave of D-Day. He had difficulty climbing in and out of the Higgins (LCVP) craft due to his concussion. He wrote, "Those of our troops who were not wax-gray with seasickness, fighting it off, trying to hold on to themselves before they had to grab for the steel side of the boat, were watching the (battleship) Texas with a look of surprise and happiness. Under the steel helmets they looked like pikemen of the Middle Ages to whose aid in battle had come some strange and unbelievable monster. There would be a flash like a blast furnace from the 14-inch guns of the Texas that would lick far out from the ship. Then the yellow brown smoke would cloud out and, with smoke rolling, the concussion and report would hit us, jarring the men's helmets. It struck your ear like the punch of a heavy, dry glove."

Figure 3. Robert Capa left, Hemingway right in France, 1944

4 Despite his official role as a correspondent, after D-Day through the liberation of Paris and into the Hurtgen Forest, Hemingway was an irregular combatant. On August 5, 1944, Hemingway was in the sidecar of a motorbike with Capa following. An anti-tank round exploded 10 yards away. Hemingway recalled, "A tank shell lifted me up and dropped me on head." He also noted that his head slammed into a boulder in the ditch. He had sustained blast wave trauma #2 and another contact trauma.

Later, with up to 200 French irregulars, Hemingway personally liberated the Ritz Hotel in Paris containing his favorite bar, now called the Bar Hemingway. He posted a guard to notify incoming friends, "Papa took good hotel. Plenty stuff in cellar."

In 1947, Hemingway received the Bronze Star, the highest award available to civilians serving with armed forces in combat areas.

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Editor's Notes (cont.)

5 On June 20, 1950, he was driving in Cuba when he lost control and slammed into an embankment cracking 4 ribs and hitting his forehead on the rearview mirror.

6 On July 1, 1950, Hemingway fell from the flying bridge on his fishing boat in Cuba, the Pilar, and hit his head requiring sutures. The doctor told him, "Being thick skulled saved your life." And he says, "That's a form of literary criticism, calling me thick skulled." He had recurrent headaches and irritability.

7 In a 1954 safari, on a chartered flight with Kilimanjaro in sight, the hydraulics of the plane failed and they were lucky to safely return to Nairobi. They then got into a Cessna 180 for the next flight. His fourth wife, Mary, wanted to photograph Murchison Falls. When the pilot dodged a flock of ibis, they hit a telegraph wire and crashed. Hemingway injured his shoulder A commercial airliner spotted crash and radioed back that there were no survivors.

They were taken by boat to Butiaba. The next day, they were taking off in a twin-engine de Havilland when they crashed. As the plane was filling with smoke, Hemingway busted open the jammed door with his head sustaining a skull fracture with left sided CSF otorrhea and a concussion.

According to the AP account, "Ernest Hemingway arrived in Entebbe today after having survived two plane crashes in the elephant country of Uganda. His head was swathed in bandages and his arm was injured, but the novelist, who is 55 years old, quipped: "My luck, she is running very good." His obituaries had been published after the erroneous report from the first crash. Mary told him, "Turn off the light, go to bed, you can't read your obituaries all night."

He wrote in a letter from Kenya on 2/2/54, "This is a funny thing. Maybe-concussion is very strange-and I have been studying it. Double vision; hearing comes and goes, your capacity for scenting (smelling something) can become acute beyond belief."

His obituaries had been published after the erroneous report from the first crash which he read with fascination. (In "Ulysses," Leopold Bloom recommended, "Read your own obituary notice; they say you live longer. Gives you second wind. New lease of life." Hemingway was James Joyce's good friend and guardian in Paris in the 1920's. They would go out to drink and Joyce would get into a fight. With his poor vision, he couldn't even see the man so he'd say, 'Deal with him, Hemingway!. Deal with him!') Many of the obituaries mentioned that he had always sought death. Hemingway asked, "Can one imagine if a man sought death all his life he could not have found her before the age of 54?"

When he received the Nobel Prize in literature later in 1954 "for his powerful, style-forming mastery of the art of modern narration," he was unable to attend as he was still recovering from his injuries. In an interview with NBC, he responded to a question about his next book provided in advance by reading slowly from cue cards as follows: "The book that I am writing on at present is about Africa, its people in the park that I know them. The animals – comma – and the changes in Africa since I was there, last – period."

In 1960, Hemingway was hospitalized at Mayo Clinic and treated with ECT. When his wife found him sitting in the kitchen holding a shotgun, he was readmitted 3 months later for more ECT in 1961. Six days after discharge, age 61, at his home in Ketchum, Idaho, Hemingway woke before sunrise and shot himself in his troubled brain with his favorite double-barreled shotgun.

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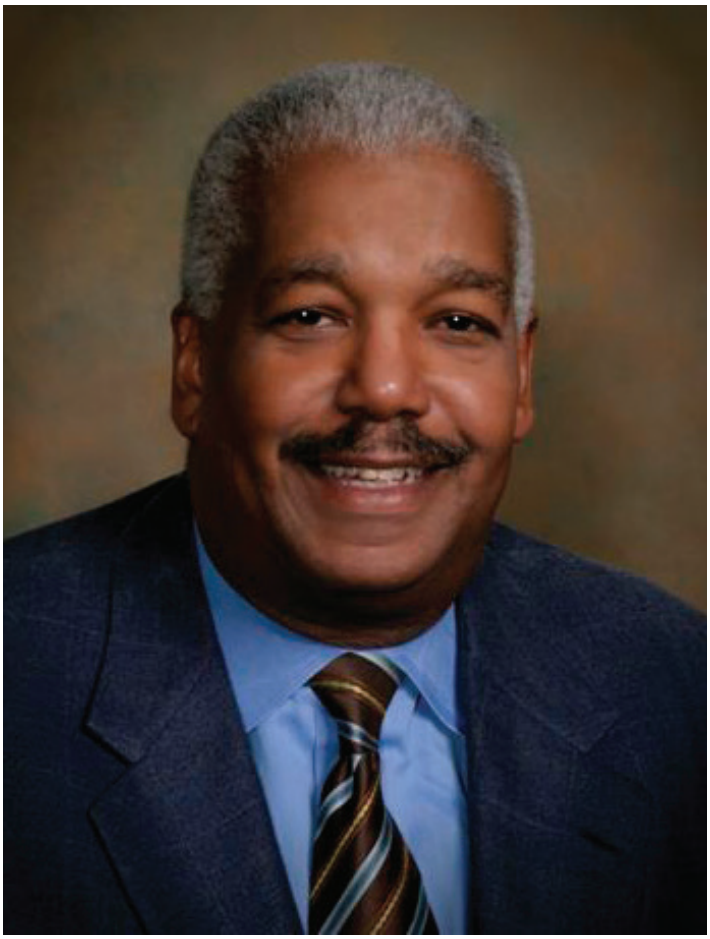
TNS Past President Receives TMA 2021 Distinguished Service Award

William H. Fleming III, MD



The Texas Medical Association honors former TMA President William H. Fleming III, MD, of Houston with the 2021 TMA Distinguished Service Award in recognition of his lifelong dedication to medicine. The award will be presented at Friday's House of Delegates meeting.

A neurologist, Dr. Fleming has spent much of his career taking on leadership positions in medicine. He has served as president of the Texas State Board of Medical Examiners, the Federation of State Medical Boards of the United States, the Texas Neurological Society, the Houston Academy of Medicine, and the Harris County Medical Society.

Dr. Fleming has also served on the Minority Affairs Consortium Advisory Board of the American Medical Association since 1999. He has been a member of the Board of Directors of the Texas Medical Liability Trust and chaired the State Affairs Committee for the American Academy of Neurology.

In 41 years as a TMA member, Dr. Fleming has served on the Board of Trustees, as speaker and vice speaker to the House of Delegates, as a delegate to the American Medical Association, and on the Council on Legislation.

A former U.S. Air Force captain, Dr. Fleming was born in Memphis, Tenn., and graduated from the St. Louis University School of Medicine in St. Louis, Mo. He held a general medicine internship at Montreal General Hospital at McGill University in Montreal. He also held a neurology residency at the Mayo Clinic and Mayo Graduate School of Medicine in Rochester, Minn.

Dr. Fleming has been awarded the National Medical Fellowships Champions of Health Distinguished Alumni Award, the Houston Medical Forum Lifetime Achievement Award, and the Texas Neurological Society Lifetime Achievement Award. *Texas Monthly* magazine three times named him a "Texas Super Doctor," and Houston Magazine twice named him a "Top Doctor."

He works as a clinical assistant professor at McGovern Medical School at UTHealth in Houston.

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TNS Legislative Update

By Dr. Sara Austin, MD, Chair, Legislative Affairs, and Tom Holloway, TNS Lobbyist

The 87th Texas Legislature has been a unique and challenging session unlike any other. Now that the House and Senate have adjourned Sine Die (the last day), the Texas Neurological Society's legislative affairs team has prepared a brief summary of how our legislative agenda fared in 2021.

SCOPE OF PRACTICE

It seems that scope of practice concerns rear their head nearly every legislative session, and this one was no different. With the filing of HB 2029, the Texas Nurse Practitioners made their strongest push yet for independent practice authority – this time with the strong support of the new House Public Health Committee Chairwoman, Representative Stephanie Klick (R-Fort Worth), a practicing nurse. However, thanks to the concerted efforts of TMA, TNS, and other physician lobby teams, HB 2029 failed to receive a vote out of Chairwoman Klick's own committee.

Another pair of bills that caused early concern to TNS are SB 293 by Senator Charles Perry (R-Lubbock) and its companion, HB 1270 by Representative Phil Stevenson (R-Wharton), which threatened to expand the practice authority of chiropractors in Texas. However, following the decision by the Texas Supreme Court which established that chiropractors who conduct vestibular-ocular-nystagmus testing (VONT) are acting within their established scope of practice (TBCE & TCA v. TMA, Jan. 29, 2021), these bills were seen as unnecessary and were not seriously pursued by their respective authors.

MD/PHD BILL

A priority piece of legislation which TNS brought forward this session is SB 1414 by Senator Joan Huffman (R-Houston), which would extend the amount of time physician scientists (MD/PhDs) have to pass their licensing examination in Texas. Currently, the Texas Medical Board's licensure examination timeline can be difficult to adhere to for physicians who are also pursuing a PhD, effectively discouraging physician scientists from becoming licensed in the state of Texas. With the help of TNS' legislative affairs team, SB 1414 passed the Senate and House and is now on its way to Governor Abbott to be signed into law.

TEXAS BRAIN INSTITUTE

This session, Representative Senfronia Thompson (D-Houston) filed HB 15 and HJR 5 to create the Brain Institute of Texas to fund research into the human brain at Texas institutions of higher education. This ambitious research program would authorize the issuance of up to $300 million in general obligation bonds over 10 years to fund the initiative. TNS has actively supported and lobbied for passage of this legislation throughout the legislative session.

While HB 15 and HJR 5 passed fairly easily through the Texas House, both have met with substantial resistance in the more conservative Texas Senate, where the $300 million price tag seemed to present the most significant stumbling block. The Senate made substantial changes in committee to address these concerns, ultimately advancing a more modest proposal that would be funded by private donations and funds appropriated by the legislature. Nonetheless, it became clear in the closing days of the session that the Lt. Governor and Senate leadership did not intend to make the Brain Institute of Texas a priority this session, and the bill ultimately died without receiving a vote before the full Senate.

MEDICAL CANNABIS

After a series of fits and starts early on, the Texas Compassionate Use Program, which governs the state's medical cannabis laws, appears poised for a significant expansion this session. HB 1535 by Representative Stephanie Klick (R-Fort Worth) would expand patient eligibility for low-THC cannabis prescriptions to include all cancer patients (as opposed to terminal cancer patients, currently allowed), patients suffering with post-traumatic stress disorder (PTSD), those with acute or chronic pain conditions for which a physician would otherwise prescribe an opioid, and others with debilitating medical conditions designated by the Department of State Health Services. The bill would also establish a compassionate-use institutional review board and amend the definition of low-THC cannabis by doubling the allowable concentration of THC from 0.5% to 1.0%.

After a strong favorable vote in the Texas House (134-12), the bill moved along to the Texas Senate where Senator Charles Schwertner, MD (R-Georgetown) worked to get the bill across the finish line line in the closing days of the session. Unfortunately, with time and political support running low, the Senate was forced to remove chronic pain from the list of eligible conditions in order to secure final passage of HB 1535. The bill is now on its way to Governor Abbott's desk for his signature.

MEDICAL BILLING TAX

A substantially early victory for TNS and the House of Medicine was the passage of HB 1445 by Representative Tom Oliverson, MD (R-Tomball) which exempts medical billing from state taxation. This bill passed with overwhelming support in both the House and Senate and has already been signed into law by Governor Greg Abbott.

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PRIOR AUTHORIZATION

While prior authorization remains a persistent headache for physicians and patients alike, this session saw some of the most significant prior authorization reform in years. HB 3459 by Representative Greg Bonnen, MD (R-Friendswood) prohibits a health maintenance organization (HMO) or preferred provider benefit plan (PPO) from requiring a physician to obtain a pre-authorization if they had previously submitted at least five pre-authorization requests for a specified health care service, and the insurer had approved at least 80% of the physician's preauthorization requests in the preceding 12 months.

While the Texas Association of Health Plans (TAHP) made every attempt to kill HB 3459, our lobby team worked with TMA and others to help Senator Dawn Buckingham, MD (R-Lakeway) advance the bill through the Senate Finance Committee and secure final passage on the Senate floor. The prior authorization "gold-carding" bill is now on its way to Governor Abbott for final approval.

TELEMEDICINE

This session, we saw a bipartisan effort to enact pay parity for telemedical services in Texas with the filing of HB 515 by Representative Tom Oliverson, MD (R-Tomball) and HB 522 by Representative Julie Johnson (D-Dallas). Unfortunately, the Texas Association of Health Plans (TAHP) appear to have successfully stopped these bills from advancing by characterizing them as an unfunded mandate on health insurance. Unfortunately, neither bill passed this session.

In more encouraging news, Representative Four Price (R-Amarillo) successfully advanced HB 4 through the Texas House – legislation that would create a clear regulatory framework for the delivery of certain healthcare services through telemedicine for patients enrolled in the Texas Medicaid program. This legislation has the potential to greatly expand the use of telemedicine in Texas and promises to be of particular help to rural Texans served by Medicaid.

Thanks to Senator Dawn Buckingham, MD (R-Lakeway) the bill moved quickly through the Texas Senate and is expected to be signed into law by Governor Abbott in the weeks ahead.

TNS would like to thank all members who testified, called or wrote letters to their legislators during this 2021 Texas Legislative Session. It is your effort that helps make the difference for the field of neurology and the house of medicine.

THANK YOU TO OUR 2021 ANNUAL WINTER CONFERENCE SPONSORS!

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Neurology on the Hill Is a Virtual Success

Bruce H. Cohen, MD, FAAN; Chair, AAN Advocacy Committee

As the new chair of the AAN Advocacy Committee, I was excited to participate in this year's Neurology on the Hill (NOH) event on May 19. Although I've participated in NOH before, this was our first ever virtual iteration of the event, which allowed me to meet with my congressional offices without having to travel to Washington, DC. Although I missed walking all over Capitol Hill in my green bow tie with my colleagues from Ohio, it was great we were still able to represent our neurology profession and our patients this year.

The first Neurology on the Hill was held in 2003 with 30 attendees, with a goal to increase awareness of issues affecting our patients and the practice of neurology on Capitol Hill and advocate for our profession's top legislative issues. There were 189 attendees total this year from 46 states, with 67 first-time attendees.

As a result of the COVID-19 pandemic, this year we talked to our members of Congress about our experiences over the past year, focusing on the following issues:

✓ **Telehealth** – by asking members of Congress to support the Telehealth Modernization Act (S. 368/H.R. 1332) and the CONNECT for Health Act (S. 1512/H.R. 2903), bills that would make permanent telehealth flexibilities implemented as a result of the COVID-19 public health emergency

✓ **Research Relief and Recovery Funding** – by asking members of Congress to support the RISE Act (S. 289/H.R. 869), a bill that authorizes $25 billion in emergency relief and recovery funds for federal science agencies, including the NIH

✓ **Medicare Patient Access** – by urging Congress to take action to avoid Medicare cuts scheduled to go into effect at the end of 2021

Much of the value of NOH occurs in the days before we visit congress – this is the time we meet with other members of our state's delegation. This is a time when the senior and junior members from other practices meet and learn from each other. This year I learned of a clinical program formed by a colleague practicing on the other side of the state and have already made a patient referral. The value of this professional bonding goes beyond words. The issues this year are all clearly patient-facing and critical for neurologists to be able to care for our patients, now and in the future. Our group felt we were effective at delivering our message and we kept the interest of our senator's staff. In a smaller group, we met with our representative and these smaller meetings are naturally more conversational because they are 1-on-1 or 2-on-1. Dr. Allison Weathers and I had a truly delightful meeting.

Don't forget, if you were unable to attend NOH this year you can contact your members of Congress too on these issues by using the AAN Advocacy Action Center. You also can see pictures from the event on social media by searching the hashtags *#NOH21* and *#AANadvocacy.*

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After having to cancel the 2020 TNS Summer Conference and meeting virtually for a great 2021 Winter Conference, we are happy to announce that our 2021 TNS Summer Conference will be held in a hybrid delivery format to accommodate in-person attendees while allowing others to participate in the meeting virtually. Please join us on July 23 and 24, 2021 at the Omni Barton Creek Hotel in Austin, TX to socialize with your colleagues and listen to the presentations by the nationally recognized speakers. The topics will include updates on the diagnostic approach and new treatments for headaches, stroke, dementia, neuromuscular emergencies, NMO-spectrum disorders, drug-induced movement disorders, as well as the updates on the topic of COVID pandemic. Ethics presentation will address the questions of brain death determination. We hope to see you in Austin!

Olga Waln, MD, 2021 TNS Summer Conference Program Director

Mark your calendars!

Lunch & Learn

July 23rd
12:00 - 12:45 pm

"Unconscious Bias in Healthcare"

Dr. Jeffrey McClean
Key leader of the AAN's Initiative towards Diversity and Inclusion

Hosted by the TNS Medical Economics committee.

TNS Social Media

Social media is a part of our communication strategy to help educate and promote the different initiatives we'll have in 2021. Connect with us on Facebook and Twitter!

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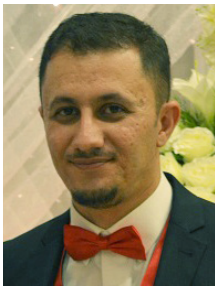

Husam Al Sultani, MD

Physicians Preferences of Virtual Versus In-Person Visits in Neuromuscular Clinical Practice

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INTRODUCTION

The use of telemedicine in clinical practice is becoming popular and many practices have adopted some form of telemedicine or plan to do so in the future[1]. COVID 19 pandemic compelled the medical community to utilize telemedicine and policies were rapidly changed to continue patient care during the pandemic[2]. While the role of telemedicine was well established in certain fields of medicine, its role in other disciplines like Neuromuscular medicine, was not as clear. There have been small scale studies that assessed satisfaction for subgroup of patients like ALS[3]. However, data on physician perspective is almost non-existent. A recent surveyed of neuromuscular patients on their preference of virtual vs in-person visits showed inclination towards in-person visits (in press), However, the opinion of the neuromuscular disorder physicians on telemedicine, is essential for understanding the future directions of tele-neurology. We designed this study to assess the opinion of neuromuscular physicians about telemedicine, their preference and factors influencing their decision.

METHOD

Study design and data collection:

We called for participants using the forum provided by Rick's real neuromuscular friends (RRNMFs), an online group of about 2000 neuromuscular disorders physicians. 94 physicians were interested. We used an online form (Microsoft Forms) composed of eleven questions to survey the interested 94 neuromuscular specialists from the USA and Canada during September 2020 (the questionnaire and consent template uploaded in Supplementary materials). The survey was conducted unanimously, surveyed physicians consented to participate in the study, and their personal information was kept discrete. We conducted a descriptive analysis of the data.

The primary outcome, neuromuscular physician visit preference, was assessed by the survey item "When you see a new patient, what type of visit do you prefer?". Responses were categorized as 'Physical (face-to-face)', 'Virtual (through the phone or video-audio system)', or 'No preference'. The second question was "When you see a follow up patient, what type of visit do you prefer?". Responses were categorized as 'Physical (face-to-face)', 'Virtual (through the phone or video-audio system)', or 'No preference'. Each question had 3 categories of responses.

RESULTS

62.77% (n=59) were males, 32.98% (n=31) were females and 4 participants declined to declare their gender. 59.57% (n=56) were younger than 50 years old, 37.23% (n=35) were older than 50 years old while three declined to answer. Regarding the type of practice, 53.19% (n=50) worked in an academic-based practice while 18.09% worked in a group practice, 15.96% worked in hospitals, 5.32% in large HMO, and 6.38% in solo-based practices (table 1).

Practice type	Percentage of total	Number of participants
Academic based	53.19%	50
Group practice	18.09%	17
Hospital based	15.96%	15
Large HMOs	5.32%	5
Solo practice	6.38%	6
Declined to answer	1.06%	1
Grand Total	**100.00%**	**94**

Table 1: *numbers and percentages of participants of the study divided according to their type of practice.*

Considering seeing new patients, 90.43% (n=85) of the participants preferred physical visits, 4.26% (n=4) preferred virtual visits while the rest had no preference or declined to answer. In response to their preference in seeing follow up patients, 44.68% (n=42) preferred physical visit, 28.72% (n=27) preferred virtual visits while 25.53% (n=24) had no preference. Moreover, 45.74% (n=43) of the participants said that practicing telemedicine had no influence on the number of procedures like EMG and biopsies, while 38.30% (n=36) thought it would decrease them, and 13.83% (n=13) thought it would increase them. The majority thought that telemedicine reduces revenue 58.51% (n=55), while 27.66% (n=26) declared no effect on revenue, and 12.77% (n=12) though it would increase revenue. When participants were asked about the quality of service, 57.45% (n=54) answered in the negative, 24.47% (n=23) said telemedicine had no effect on the quality of service, while 17.02% (n=16) thought that the quality of service would improve. 44.68% (n=42) somewhat agreed that quality time spent with patients would be reduced, 18.09% (n=17) strongly agreed with the previous statement, while 36.17% (n=34) disagreed. Most

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Percentage of total (n)	New patient preference	Follow up patient preference	Revealing new diagnosis
No preference	3.19% (3)	25.53% (24)	23.40% (22)
Physical visits	90.43% (85)	44.68% (42)	75.53% (71)
Virtual visits	4.26% (4)	28.72% (27)	00.00% (0)
Total	**(92)**	**(93)**	**(93)**

Table 2: *physician preference of the study type and revealing a new diagnosis*

Percentage of total (n)	Influence of telemedicine on number of procedures	Influence of telemedicine on revenue	Influence of telemedicine on the quality of services	Influence of telemedicine on workload
Increase in numbers/ Revenue/quality	38.30% (36)	58.51% (55)	17.02% (16)	13.83% (13)
Decrease in numbers/ Revenue/ quality	13.83% (13)	12.77% (12)	24.47% (23)	26.60% (25)
No effect	45.74% (43)	27.66% (26)	57.45% (54)	58.51% (55)
Total	**(92)**	**(93)**	**(93)**	**(93)**

Table 3: *Subjects opinion on number of procedures, revenue, service quality, and workload*

Percentage of total (n)	telemedicine will reduce the quality time with patients	Telemedicine is time-efficient	Telemedicine will improve patient's compliance
Strongly agree	18.09% (17)	26.60% (25)	18.09% (17)
Somewhat agree	44.68% (42)	57.45% (54)	52.13% (49)
Disagree	36.17%	14.89% (25)	28.72% (27)
Total	**(93)**	**(93)**	**(93)**

Table 4: *Subjects opinion on the effect of telemedicine on the reduction of quality time with patients, time-efficiency, and improving patient's compliance*

Percentage of total (n)	
During the pandemic only	31.91% (30)
Long term solution	62.77% (59)
Not efficient at all	4.26% (4)
Total	**(93)**

Table 5: *Telemedicine efficiency during COVID-19 pandemic versus a long-term solution*

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surveyed physicians agreed that telemedicine was time-efficient: 57.45% (n=54) somewhat agreed, and 26.60% (n=25) strongly agreed, while 14.89% (n=14) disagreed. 52.13% (n=49) somewhat agreed that telemedicine improved patient compliance, 18.09% (n=17) strongly agreed, while 28.72% (n=27) disagreed. 62.77% (n=59) declared that telemedicine would be a long-term solution in clinical practice, 31.91% (n=30) thought telemedicine was effective only during the pandemic, while 4.26% (n=4) said it was not efficient in both cases. 58.51% (n=55) revealed that telemedicine did not affect workload, while 26.60% (n=25) thought it increased workload and 13.83% (n=13) thought telemedicine decreased workload. Finally, 75.53% (n=71) preferred to reveal a new diagnosis during a physical visit, and none 0.00% during a virtual visit, while 23.40% (n=22) had no preference.

DISCUSSION:

Our study showed that the majority of the surveyed neuromuscular disorders physicians preferred in-person visits for new patients. Even for follow up visits, there was high inclination towards in-person visits (44%), but almost half the physicians either preferred virtual visits (28%) or did not have a preference (25%). The results are not surprising but differ from other surveys which have shown higher satisfaction rates and a tendency towards choosing telemedicine in future[4]. The data on physician preference is very limited and almost non-existent in the field of neuromuscular medicine. The comparative studies have key design differences. The studies done prior to COVID 19 pandemic had compared the satisfaction and feasibility of telemedicine in selected patient populations with set models[4,5]. Since the start of pandemic, physicians were forced to use telemedicine for all types of patients to provide care in the era of social distancing and we entered this practice unprepared, hence, faced multiple challenges including facing policies regarding reimbursement, lack of trained staff and equipment[1]. It affected everyone differently and our data provides how neuromuscular physicians feel about telemedicine use in future.

Adoption of telemedicine in routine clinical practice faces multiple challenges and giving this option to patients comes at a cost. Despite the new regulations of telemedicine reimbursement and matching reimbursement of the in-office visits, still, 97% of private practices reported negative financial outcomes during the pandemic[6]. Our survey showed similar results as majority (58%) physicians said that telemedicine decreases revenue. This is an important factor that will influence the implementation of telemedicine in future.

The fact that physicians preferred in-person visits for new patients, and none chose virtual visit to reveal a new diagnosis speaks about the fact the physicians are not mere diagnosticians. The first interaction with the patient is not only meant to make the best judgement about the diagnosis and exam but is also a first step to build a relationship. Preferences of this study are justified by the fact that in neuromuscular specialty, detailed neurological examination is needed, which is not feasible virtually, and neurophysiology is often used as an extension of the physical examination. Most neuromuscular conditions are chronic and require long term care. To build rapport with the patient, gestures, face to face interaction, assessing personality and patient expectation, it is best done in-person. This is compromised in telecommunication. With advancement in technology and more preparation to facilitate virtual interaction, the opinion is subject to change.

Despite physicians choosing in-person visits, majority agree that telemedicine will be a long term solution and does not affect quality of service. This indicates that in physician opinion, there may be role of telemedicine but in selected patient population. One main limitation of our survey is that we do not have data on the challenges and limitations faced by each practice and if influenced the decision of choosing visit type. Since COVID 19 pandemic affected each practice differently, the barriers faced by one practice and hence the translation to workload, quality of care might be different. It will be helpful to know the individual challenges to come up with a solution.

In conclusion, despite the preference of telemedicine in many specialties of healthcare practices, neuromuscular physicians still prefer face to face visits especially in seeing new patients emphasizing the distinct nature and peculiarities of neuromuscular disease specialty. While preferences for new patients and breaking new diagnoses clearly favored physical visits, such preference only marginally favored follow up visits. While most of the participants agreed that telemedicine improved patient's compliance and it was time efficient solution, they still had doubts about the economic factors and quality of service and time spent with patients. COVID-19 pandemic imposed difficult questions in clinical practice, and while healthcare facilities and physicians showed flexibility in dealing with the new norms[7], the prospect of the sudden change might take clinicians from the comfort routines. Neuromuscular specialists preferred seeing new patients and revealing new diagnosis to patient in physical visits, but they also considered telemedicine a long-term method that would continue to increase in the post-pandemic future[8]. There was a crucial need to stimulate neuromuscular practices to adopt telemedicine by addressing their concerns and boost the positive factors like continuing the current insurance policies and the patient privacy flexibility.

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Mild Encephalitis/Encephalopathy with a Reversible Splenial Lesion (MERS) Associated with Systemic Mycoplasma pneumoniae Infection In North America; A Clinical Case Report

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AUTHORS' CONTRIBUTIONS

NT, AF, and JL all contributed to collecting information regarding the case, writing the article, and for the design of the present study. All authors read and approved the final manuscript.

PATIENT CONSENT FOR PUBLICATION

Consent for publication was obtained from the patient's parents (mother) of this study.

COMPETING INTERESTS

The authors declare that they have no competing interests and do not have any financial disclosures.

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ABSTRACT

MERS is a clinical-radiological entity found to occur in the setting of an acute systemic inflammatory state with isolated lesions of the SCC and mild encephalopathy. Most commonly found to occur in children, secondary to a viral infection. Only a few cases of MERS associated with MP have been reported in the US, relative to Eastern and Southern Asia. We present the case of a 5-year-old boy with ASD presenting with acute onset intractable vomiting, diarrhea, and frequent tensing episodes, ultimately discovered to have MERS secondary to acute MP systemic infection, demonstrating complete resolution with inadequate antimicrobial coverage and a single administration of pulse-dose steroids.

BACKGROUND

Mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) is a clinical-radiological entity found to occur in the setting of an acute systemic inflammatory state with isolated lesions of the splenium of the corpus callosum (SCC) on Brain Magnetic Resonance Imaging (MRI) and in a mild encephalopathic state[1]. Most commonly seen in children, the presentation is generally non-specific and can range from irritability to alterations of consciousness[2]. The most common etiologies are thought to be related to seizures, metabolic changes, or infections. Most cases are associated with viral infections[3]. While cases linked to bacterial infections have been found in the literature, only a few cases of MERS associated with Mycoplasma *pneumoniae* (MP) have been reported; and of those, most are reported in Eastern Asian countries[4]. MP is an atypical bacterium responsible for a significant proportion of respiratory tract infections in children[5], and is found to be responsible for up to 10% of pediatric encephalitis cases[6]. Though ubiquitous in the community, only a handful of MP-associated MERS cases have been reported in the United States (US). We present the case of a 5-year-old boy with Autism Spectrum Disorder (ASD) in the US presenting with intractable vomiting, diarrhea, and frequent tensing in the setting of MP-associated MERS.

CASE REPORT

A 5-year-old boy with ASD and speech delay presented to our emergency department (ED) with decreased oral intake in the setting of intractable vomiting and diarrhea along with abnormal movements, for the past 2 days. As per his mother, he initially began to display symptoms of fatigue, fever, and spastic abdominal pain 6 days ago shortly after these same symptoms occurred in his cousin and his younger brother; the latter of which presented with a simple febrile seizure and was discharged home from the ED without further neurologic changes. They initially presented to an outside ED 6 days ago, where he was diagnosed with viral gastroenteritis and discharged home. However, over the past two days, the patient had become more somnolent with generalized weakness, and developed over 20 episodes of full body tensing, with bilateral upper extremity flexion and lower extremities extension lasting 5-10 seconds per episode. Mother felt as if these were temporally correlated with his spastic abdominal pain, as he was screaming out crying during these episodes. She additionally noted mild improvement with over-the-counter antipyretics, however, he remained lethargic and irritable. Upon arrival at our ED he was agitated, with generalized weakness, refusing to move, with a fever of 102 degrees Fahrenheit. Emergent evaluation by Pediatric surgery with abdominal

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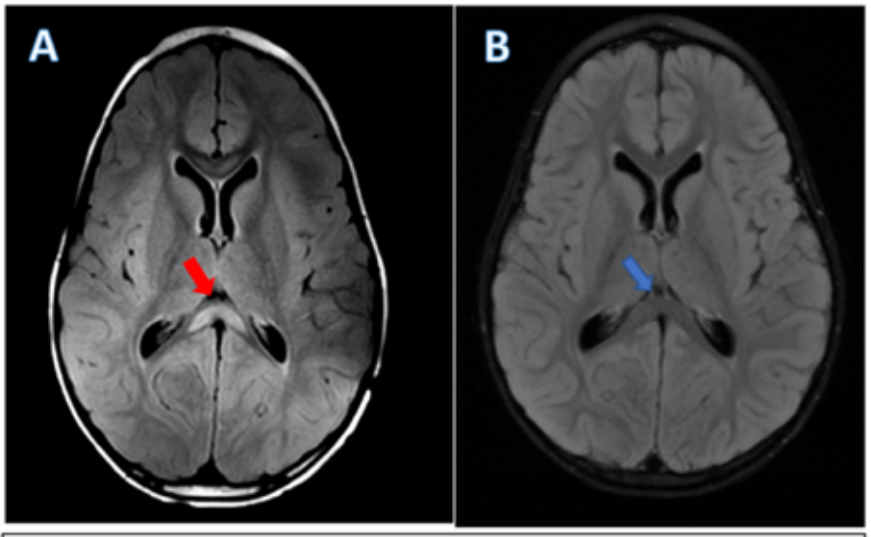

Figure 1. MRI Brain T2 Fluid Attenuated Inversion Recovery (FLAIR) sequence demonstrating A. hyperintensity involving splenium of the corpus callosum (red arrow), aka "Boomerang Sign"[16], with B. resolution of hyperintense signal on repeat imaging after 5 days (blue arrow) since initial imaging and 2 days after pulse-dose intravenous steroid.

X-ray, ultrasound, and MRI ruled-out acute surgical abdomen, intussusception, or appendicitis. Infectious disease was initially consulted given concern for encephalitis or meningitis in the setting of fevers, intractable vomiting, and increased irritability and lethargy. He was started on empiric meningitic doses of vancomycin, ceftriaxone, and acyclovir. An MRI Brain obtained by his primary team noted an isolated SCC hyperintensity on T2 Fluid-Attenuated Inversion Recovery (FLAIR) sequence (figure 1A); read as "possible postictal changes" by the radiologist. Cerebrospinal fluid (CSF) profile from lumbar puncture (LP) demonstrated a neutrophilic pleocytosis with elevated protein and normal glucose, concerning for possible viral meningitis.

Pediatric Neurology was consulted regarding encephalopathy with reported abnormal repetitive movements, MRI changes, and CSF with inflammatory profile. Upon examination, he was lethargic, agitated, refusing to change positions. 48 hours of continuous video electroencephalogram (cvEEG) was completed, which was only notable for mild diffuse encephalopathy. Multiple brief tensing episodes were captured along with 3 brief desaturation episodes, all of which were without electrographic correlates, however, did correlate to patient screaming and clenching his stomach; thus, the most likely etiology of his fits was determined to be pain-related, rather than seizures. Results from his infectious work-up slowly began to return. Regarding his CSF cultures, streptococcus pneumoniae antigen, enterovirus, and herpes simplex virus (HSV) polymerase chain reaction (PCR) was negative; and his empiric acyclovir was discontinued after 2 days of treatment. In addition, viral respiratory PCR testing, COVID-19 nucleic acid amplification (NAA), blood cultures, and stool studies were all negative for the identification of the pathogen. Serological studies were sent soon after admission, with tests for Epstein-Barr Virus, HIV, Bartonella Henselae, Bartonella Quintana negative prior to discharge.

Multidisciplinary discussions determined the patient likely had MERS in the setting of post-viral, or post-infectious, systemic inflammatory changes. Based on literature review, the decision was made to administer a one-time pulse-dose of intravenous (IV) methylprednisolone at 20mg/kg. The patient demonstrated gradual improvement in his movement and mood following his corticosteroid dose; he began to eat more and ultimately returned back to baseline. A repeat MRI brain and LP 5 days after his initial presentation and imaging demonstrated complete resolution of the SCC lesion (figure 1b) and inflammation in the CSF. His mother endorsed he was back to his neurologic baseline with only a mild decrease in oral intake due to his oral thrush. He was discharged home with home PT and close outpatient follow-up with his pediatrician and pediatric neurology. He completed 5-days of antibiotics, and as patient returned back to baseline and remained without fever, vomiting, or diarrhea he was discharged home without antibiotics. Following discharge, the patient's remaining serological labs returned, which demonstrated an acute MP infection with elevated IgG (2.28, normal <0.9) and IgM antibody (786U/mL, normal <770U/mL).

DISCUSSION

Since its initial description in 2004 by Tada et al., based on a case series of 15 patients presenting with encephalitis/encephalopathy with isolated lesions in the SCC on brain MRI[1], multiple cases of MERS have been reported in the literature; yet much remains unknown. Prevalence is seemingly higher in the pediatric population, though multiple cases have been reported in adults as well. In the pediatric population, MERS is thought to be more of an infection-associated encephalopathy syndrome[7]. While

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associations with other systemic conditions such as metabolic derangements like hyponatremia and hypoglycemia, postictal, withdrawal of anti-seizure medications, high-altitude cerebral edema, and immune-mediated systemic inflammatory disorders such as systemic lupus erythematosus, have been reported more in adults[1,2,7,8]. There are no known associations of direct central nervous system (CNS) infection or inflammation with the occurrence of MERS; rather, these changes are more likely to be caused by inflammatory changes in the setting of non-CNS infections[2]. Its presentation is often non-specific, with the most common presenting neurological symptoms involving delirious behaviors, disturbances in consciousness, irritability, and even seizures[1,3,4].

The most common causative infectious organisms associated with MERS are viruses, such as Influenza A and B, Rotavirus, Adenovirus, Respiratory Syncytial Virus (RSV), HSV, with one documented case associated with COVID-19 infection[2,7,9]. Bacterial etiologies are reported less commonly, although reports of MERS in association with E.coli O-157, Salmonella typhi, Streptococcus pneumoniae, and Legionella have been reported[1,3,9,10]. Our patient was ultimately diagnosed with MERS associated with a systemic MP infection. MP is an atypical bacterium with the inability to synthesize peptidoglycan cell walls; thus, confers natural resistance against beta-lactam and glycopeptide antibiotics, such as cephalosporins and vancomycin, respectively, as they specifically target cell wall biosynthesis[11,12,13]. This small, atypical bacterium is ubiquitous in the community and is a common respiratory tract pathogen affecting children. It is responsible for up to 40% of community-acquired pneumonia in children between the ages of 5-14[5], and up to 10% of pediatric encephalitis cases[6]. Additionally, symptoms can vary in children, with those greater than 5 years of age more commonly present with fever, chills, sore throat, and progressive cough; while children 5 years old and below can present with atypical symptoms, such as the vomiting and diarrhea seen in our patient[14]. Despite infection being so rampant in the pediatric community, very few cases of MP-associated MERS in the US have been reported relative to Eastern and Southern Asian countries such as China, Japan, and India[3,10]. This may, in part, be explained by the discrepancy in the prevalence of Macrolide-Resistant MP (MRMP) between these 2 regions, with a resistance rate of up to 80-90% in Eastern Asia compared to about 10% in the US[4,14]. Infections with MRMP have been reported to be greater in severity and longer in duration, and this amplified state may suggest a correlation between intensity of inflammatory response and MERS[4]. Given the rarity of MP-associated MERS reported in the US, much remains unknown regarding its presentation, predilection, and treatment strategy.

Overall, MERS carries an extremely favorable prognosis; with complete resolution of symptoms between 3 to 19 days for type 1 MERS, lesions limited to the SCC, and up to 3 to 6 months in patients with type 2 MERS, which involves the entirety of the corpus callosum[5,10]. The lack of controlled trials assessing effectiveness of therapeutic models and our limited understanding of the mechanisms underlying CNS involvement of MP-associated MERS has led to rather elusive treatment strategies.

When associated with systemic infection, MERS is thought to result from an immune-mediated reaction of the body to the inciting pathogen[6]. This raises the question if solely treating the underlying pathogen is by itself sufficient, if immunomodulatory therapy is curative or beneficial, or if the syndrome itself self-resolves spontaneously. Our patient was treated with 5 days of beta-lactam and glycopeptide antibiotics, without a macrolide, fluoroquinolone, or tetracycline antibiotic treatment, which are considered first-line agents for MP[14]. Despite inadequate microbial coverage, our patient demonstrated complete resolution of his symptoms, imaging changes, and inflammation in the CSF within 5 days upon admission: and about 11 days since initial symptoms onset. His infection was untreated from a pharmacotherapeutic perspective; thus, our outcome questions the need for antibiotics in the management of MERS. The effect of antibiotics in MP infections overall remains a controversial topic based on prospective studies and retrospective analysis during epidemics of MP[4]. They are often self-limiting; however, they continue to be treated routinely with antibiotics. While antibiotics may have limited effects on MP infection as a whole, early corticosteroid use in cases of pneumonia due to MP has demonstrated a reduction in morbidity and mortality, and prevention of severe disease progression[4]. The lack of controlled trials or systematic reviews has led to ambiguity in the approach to treating MP-associated encephalitis as well. Similar to MERS, this entity is thought to have an immunological origin. Several immunomodulatory therapeutic measures have been reported for treatment, including intravenous immunoglobulin, plasmapheresis, and corticosteroids[6]. All patients in these reported cases, regardless of treatment strategy, demonstrated a full recovery and reversal of MRI signal changes[4,6,15]. While prospective and retrospective analysis demonstrate overall benefit from corticosteroid use in pneumonia due to MP, use of systemic steroids have often been proposed for treating extrapulmonary manifestations, particularly conditions involving the central nervous system; however, data is limited on its potential benefits[15].

The self-limited nature of MP infections and the lack of standardized controlled studies underlie our limitations in the approach of managing these conditions. Our patient demonstrated complete resolution following inadequate antimicrobial coverage and one dose of pulse-dose steroids raising the question of whether our therapy was the driving force for his recovery. If so, would our findings suggest that sole corticosteroid therapy is sufficient to mitigate the inflammatory effects secondary to MP-associated MERS. Would our patient have recovered in due time without any intervention, and does corticosteroid therapy affect rate of recovery? In essence, much remains unknown regarding the management of this condition. Further studies in the US remain a challenge given the limited number of cases reported for MP-associated MERS. As antibiotic use, or even overuse, continues, rates of macrolide resistance in MP will continue to rise in the US; maintaining a keen sense of awareness will remain key to unlocking further understanding for this unique phenomenon.

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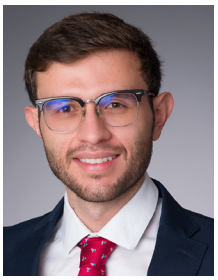

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Parkinson's Disease Treatment: An Brief Update and Review

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INTRODUCTION

Parkinson's disease (PD) is the second most prevalent neurodegenerative disease behind Alzheimer's disease (E. R. Dorsey et al., 2007). It is estimated that around 6.1 million people received a diagnosis of PD in 2016, with an approximate prevalence of 930,000 cases in the United States in 2020 (Armstrong & Okun, 2020; Marras et al., 2018)a group of neurological disorders with Parkinson disease-like movement problems such as rigidity, slowness, and tremor. More than 6 million individuals worldwide have Parkinson disease. Observations: Diagnosis of Parkinson disease is based on history and examination. History can include prodromal features (eg, rapid eye movement sleep behavior disorder, hyposmia, constipation. With an aging population and more specifically, an increasing proportion of patients over 65 years, it is expected that by 2040 the number of people with PD globally will exceed 12 million (E. Ray Dorsey & Bloem, 2018).

Understanding the pathophysiology of PD and its symptoms has led to the development of a substantial armamentarium of therapeutic strategies aimed at improving the quality of life for patients afflicted with the disease. Most cases of PD are sporadic and likely due to both environmental and genetic influences. It has been widely recognized that the pathologic hallmark of PD are Lewy bodies, which are thought to lead to the death of dopaminergic neurons in the substantia nigra pars compacta. Aggregated oligomeric α-synuclein is the primary constituent of Lewy bodies and thought to produce neuronal dysfunction by negatively impacting ve-

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sicular transport, the lysosome-autophagy system, mitochondrial homeostasis, and by producing oxidative stress (Fields, Bengoa-Vergniory, & Wade-Martins, 2019). Currently many drug development initiatives for PD treatment are targeting these cellular processes.

Different hypotheses regarding the progression of PD have been proposed, with some suggesting alpha-synuclein aggregation may begin outside of the central nervous system. One of the first proposed mechanisms, known as the Braak hypothesis, postulates that some sites of initial α-synuclein deposition are the olfactory nucleus, the dorsal IX/X motor nuclei, and/or intermediate reticular zone in the brainstem after which it spreads rostrally towards other structures; a plausible reason for why some non-motor symptoms such as REM sleep behavior disorder and olfactory dysfunction may precede the onset of motor symptoms by a decade or more (Braak et al., 2003). A more recent hypothesis suggested that pathological forms of α-synuclein can mimic a prion-like propagation, thus affecting neighboring cells (Shahnawaz et al., 2020). Also, some studies have proposed that pathogenic forms α-synuclein can originate in the gut and ascend through the vagus nerve towards the brain, affecting sympathetic and parasympathetic systems along the way (Kim et al., 2019). Additionally, it is widely recognized that neurotransmitters such as serotonin, acetylcholine, and norepinephrine may affect many of the nonmotor symptoms in PD, which are often unresponsive to treatment with dopaminergic therapies (Armstrong & Okun, 2020)a group of neurological disorders with Parkinson disease-like movement problems such as rigidity, slowness, and tremor. More than 6 million individuals worldwide have Parkinson disease. Observations: Diagnosis of Parkinson disease is based on history and examination. History can include prodromal features (eg, rapid eye movement sleep behavior disorder, hyposmia, constipation.

In this review, we briefly discuss the various strategies that are currently employed to treat the motor and non-motor symptoms of PD. We also mention some of the proposed interventions for which evidence is still lacking, as well as highlight future possibilities for the development of novel therapies.

TREATMENT OF MOTOR SYMPTOMS

Since its discovery over 50 years ago, levodopa remains the gold-standard for the motor symptoms such as bradykinesia, rigidity and tremor (Warren Olanow et al., 2013)the STRIDE-PD study population was investigated to determine the effect of l-dopa dose and other risk factors on the development of dyskinesia and wearing-off. Patients were randomized to receive LCE (n=373. After much debate, recent research supports the use of levodopa as a first line agent. The PD-MED study (Gray et al., 2014) demonstrated that initiating levodopa-sparing medications, such as monoamine oxidase B (MAOB) inhibitors or dopamine agonists versus levodopa, led to a higher rate of discontinuation of treatment (Espay & Lang, 2017), which ultimately culminated in compromise of activities of daily living (Gray et al., 2014). Despite inevitable levodopa-induced dyskinesias, levodopa use is associated with higher functional improvement. Novel formulations and routes of administration, including sublingual and inhaled, among others, allow for an easier access and increased adherence (Freitas, Ruiz-Lopez, & Fox, 2016; Patel & Jimenez-Shahed, 2018). MAOB inhibitors and dopamine agonists have a lower risk of dyskinesias, however, as monotherapy, provide less global symptom relief and higher overall risk of adverse events. In patients with early-onset PD, especially when tremor is a predominant symptom, the use of anticholinergics, such as trihexyphenidyl, can be considered as an option. However, the potential for adverse events associated with anticholinergics, principally those related to cognition (Armstrong & Okun, 2020)a group of neurological disorders with Parkinson disease-like movement problems such as rigidity, slowness, and tremor. More than 6 million individuals worldwide have Parkinson disease. Observations: Diagnosis of Parkinson disease is based on history and examination. History can include prodromal features (eg, rapid eye movement sleep behavior disorder, hyposmia, constipation, must be monitored closely.

Adjunct medications are appropriate when patients begin to experience motor fluctuations. Enzyme inhibitors, targeting the breakdown of levodopa, are recommended once patients begin to experience "off" periods. It has been suggested that, for practical purposes, combination therapy should be considered for patients who require ≥5 daily doses of levodopa (Antonini et al., 2018). Additionally, if the beneficial effect of levodopa or the "on" time lasts less than 3 hours, shortening the dosing intervals may not be satisfactory in the long term (Fabrizio Stocchi, 2006). Catechol-O-methyltransferase (COMT) inhibitors are commonly used to increase the area under the curve of levodopa and therefore, optimize "on" time. Tolcapone and entacapone are amongst the most widely studied COMT inhibitors, although concerns regarding hepatotoxicity have limited the use of tolcapone. To date, tolcapone use has been restricted to experienced physicians in the management of PD and requires strict monitoring of hepatic function and is initiated only after demonstrated intolerance or therapeutic failure of other COMT inhibitors. The need for a novel COMT inhibitor with an improved pharmacodynamic profile led to the development of opicapone, which has shown a sustained effect with decreased motor fluctuations in patients with PD (Müller, 2015). Moreover, istradefylline, an adenosine A_{2A} receptor antagonist has shown to decrease "off" times and improve motor symptoms in PD, and is used concomitantly with levodopa formulations (Sako, Murakami, Motohama, Izumi, & Kaji, 2017). As adjunctive therapy, there is evidence that the MAOB inhibitor rasagiline can be more effective than the COMT inhibitor entacapone in reducing motor symptoms during the "off" time, decreasing the UPDRS motor score in 4.38 points on average. This difference was explained by the irreversible inhibition of MAOB, which results in a longer duration of effect compared to the short half-life of entacapone (F. Stocchi & Rabey, 2011). Although no head-to-head studies have been done comparing the FDA-approved MAOB inhibitors selegiline and rasagiline, a better safety profile in the elderly and no dietary restrictions have made rasagiline the best in compliance among PD medications. Safinamide, another MAOB inhibitor with antiglutamatergic effect, received the FDA approval in 2017 and has shown to have antidyskinetic effects

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(Dezsi & Vecsei, 2017).

For patients who develop dyskinesias associated with dopaminergic medications, either dose reduction – which may exacerbate parkinsonism – or amantadine may be considered to mollify this side effect (Fox et al., 2018). If discontinuation of dopamine agonists is needed, this should be done slowly as patients may develop withdrawal symptoms (e.g., anxiety, panic attacks, irritability), especially in those who present with impulse control disorders secondary to dopamine receptor agonists such as ropinirole and pramipexole (Armstrong & Okun, 2020; Garcia-Ruiz et al., 2014) ropinirole, or rotigotine.

Apomorphine injections and inhaled levodopa are useful for treatment of "off" periods, and each can be used up to five times per day (LeWitt et al., 2019; Pessoa, Moro, Munhoz, Teive, & Lees, 2018). A sublingual apomorphine film was recently approved for the management of "off" periods and was found to be efficacious, with mainly oropharyngeal side effects such as mucosal erythema and dry mouth (C. Warren Olanow et al., 2020). Apomorphine is an effective rescue therapy for the treatment of motor symptoms in PD, but it has also proven to control various non-motor symptoms such as hyperhidrosis, nocturia, urgency of micturition, and fatigue (Martinez-Martin et al., 2011)UPDRS 4 ($p = 0.0003$. Furthermore, in advanced stages of PD, apomorphine can be delivered as a continuous infusion using a portable pump (Pfeiffer, Gutmann, Hull, Bottini, & Sherry, 2007)APO at their TED+0.2 mL (2.0 mg; APO+2. Orally inhaled levodopa has been approved to be used during "off" periods, with faster higher concentrations of plasma levodopa compared to oral dosing of carbidopa/levodopa (Lipp, Batycky, Moore, Leinonen, & Freed, 2016)such as rapid onset of action, but require formulations and delivery systems that reproducibly and conveniently administer the drug. CVT-301 is a powder formulation of levodopa delivered by a breathactuated inhaler that has been developed for treating OFF episodes (motor fluctuations between doses of standard oral levodopa. Additional studies have shown that its absorption is not altered by food intake (Safirstein et al., 2020)LD use is complicated by a progressive shortening of the duration of efficacy of a dose, resulting in episodes of inadequate responsiveness, or OFF periods. OFF periods may also occur unpredictably, partly due to the pharmacokinetic (PK.

As PD progresses, despite being responsive to pharmacologic therapy, patients may develop dyskinesias or "off" periods that are no longer treatable with medication adjustments. For this type of patient, interventions such as deep-brain stimulation (DBS), MRI-guided focused ultrasound, and levodopa-carbidopa enteral suspension can be offered.

DBS is a neuromodulation-based surgical procedure that aids in the management of motor fluctuations, levodopa-induced dyskinesia, and drug-resistant tremor (Deuschl et al., 2006). Although the exact mechanism for its effect has not been completely unveiled, evidence suggests that DBS could act by inhibiting action potentials, participating in the release of neurotransmitters, or disrupting abnormal rhythmic neuronal firing (Herrington, Cheng, & Eskandar, 2016). Stimulation of different nuclei have proved to exert different effects in patients with PD. Targeting the thalamic ventral intermediate nucleus resulted in an average tremor reduction of over 80% (Benabid et al., 1998; Benazzouz et al., 2000), however, this is not a target used regularly for PD. Subthalamic nucleus stimulation can result in improvement of gait, tremor, rigidity, and bradykinesia (Anderson, Burchiel, Hogarth, Favre, & Hammerstad, 2005; Benabid et al., 1998). Stimulation of the globus pallidus internus can help with the reduction of rigidity and akinesia, as well as levodopa-induced dyskinesias, with its posteroventrolateral region identified as the most efficient area of stimulation (Benabid et al., 1998; Laitinen, Bergenheim, & Hariz, 1992).

Despite these therapeutic benefits, careful consideration needs to be given to appropriate patient selection. DBS for PD is generally contraindicated in individuals with a lack of levodopa responsiveness, intractable or untreated psychiatric symptoms, dementia, atypical parkinsonism, and multiple comorbidities amongst others (Katz, Kilbane, Rosengard, Alterman, & Tagliati, 2011). Potential intraoperative adverse effects of the electrode implantation DBS are asymptomatic intraventricular hemorrhage (3.4%) and symptomatic intracerebral hemorrhage (1.1%). Headache (4.2%), hemiparesis (1.7%), and confusion (1.0%) are the most common perioperative (≤2 weeks) complications (Fenoy & Simpson, 2014) the community at large continues to be hesitant about presumed associated risks. The main object of this study was to assess the incidence of various surgical complications occurring both during and after DBS device implantation in a large population of patients with movement disorders in an effort to better quantify patient risk, define management plans, and develop methods for risk avoidance. A second aim was to corroborate the low procedural complication risk of DBS reported by others, which in light of the procedure's efficacy is needed to promote its widespread acceptance. Methods. All patients who had undergone new DBS device implantation surgery between 2002 and 2010 by a single surgeon were entered into a database after being verified by cross-referencing manufacturer implantation records. All surgical records and charts were reviewed to identify intraoperative, perioperative, and long-term surgical complications, including any characteristics predictive of an adverse event. Results. Seven hundred twenty-eight patients received 1333 new DBS electrodes and 1218 new internal pulse generators (IPGs. An increased risk of adverse outcomes exists in patients older than 75, those with cognitive impairment, and patients who present with levodopa-unresponsive symptoms (i.e., gait, balance, and speech impairments) (Martinez-Ramirez & Okun, 2013; Moro et al., 2016). The duration of DBS efficacy has not been precisely calculated, but a sustained benefit can exist for at least 10 years (Rizek, P. Kumar, N. Mandar, 2016).

MRI-guided focused ultrasound has been approved for the management of tremor in patients with PD, and some studies have hypothesized that it could also be useful for controlling other non-motor symptoms (Lennon & Hassan, 2021). This procedure involves targeting the thalamus with ultrasonic beams and is only done unilaterally to prevent impairment in functions such as speech and balance. Ultrasonic therapy has been shown to improve tremor scores by 62% at 3 months after the procedure (Bond et al., 2017).

An advanced therapeutic pharmacological option is treatment with an enteral suspension of carbidopa/levodopa, which is delivered percutaneously to the proximal jejunum. Thus, the

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medication bypasses gastric emptying and improves intestinal absorption, with evidence demonstrating reduced motor fluctuations and improved quality of life in patients with advanced PD (Charles W. Olanow et al., 2014). Adverse events related to this procedure may include complications with device insertion, abdominal pain, and tube displacement (Wirdefeldt, Odin, & Nyholm, 2016).

Non-pharmacological interventions such as gait and balance training, resistance training, treadmill exercise, aerobic exercise, and music and dance-based approaches have shown to help improve motor symptoms in PD (Chung, Thilarajah, & Tan, 2016; Mak, Wong-Yu, Shen, & Chung, 2017; Mehrholz et al., 2016) and reducing the risk of falls (Canning et al., 2015). Physiotherapy, occupational therapy, and speech therapy are also incredibly important and should be used early in the course to engrain compensatory strategies (Armstrong & Okun, 2020)a group of neurological disorders with Parkinson disease-like movement problems such as rigidity, slowness, and tremor. More than 6 million individuals worldwide have Parkinson disease. Observations: Diagnosis of Parkinson disease is based on history and examination. History can include prodromal features (eg, rapid eye movement sleep behavior disorder, hyposmia, constipation. The Lee Silverman Voice Treatment (LSVT) programs LOUD – for speech therapy – and BIG – to address limb motor systems – have been researched for more than 20 years and focuse on increasing amplitude of sounds and movements, sensory readjustment, and maintenance of outcomes. The BIG program has demonstrated to increase in 12-14% the velocity of gait and reaching movements (Farley & Koshland, 2005), and there is evidence of a mean improvement of 5.05 points in the UPDRS motor score (Ebersbach et al., 2010). Regarding boxing programs, despite existing reports of positive outcomes in PD, a recent systematic review concluded that they still need to be evaluated for their real benefits, precautions, contraindications, and limitations, as well as clarifying the structure in terms of duration and intensity of training (Morris et al., 2019). Preliminary results of the Rock Steady Boxing program showed that it could improve quality of life and non-motor symptoms in PD such as fatigue, depression, and anxiety (Larson, Yeh, Rafferty, & Bega, 2020).

TREATMENT OF NONMOTOR SYMPTOMS

For depressive symptoms, the selective serotonin reuptake inhibitors (SSRIs) are routinely used to treat depression and anxiety in PD. The dopamine agonist pramipexole, and the selective serotonin norepinephrine inhibitor venlafaxine, have been specifically studied in PD and are considered efficacious and clinically useful. Practically, the SSRIs are widely used for depression and anxiety, relatively common nonmotor symptoms in PD. Regarding PD-associated dementia, acetylcholinesterase inhibitors have been studied with conflicting evidence regarding their benefits. Despite studies evaluating the efficacy of rivastigmine, donepezil, and galantamine for the management of PD-associated dementia, rivastigmine remains as the only FDA-approved medication for this condition (Goldman & Holden, 2014). Worsening tremors or cholinergic symptoms should be monitored periodically. Rivastigmine has also shown to be useful for the treatment of apathy in PD (Thobois et al., 2013).

In patients with PD who present with psychosis, management should include, if possible, cautious down titration of potentially offensive medications, such as anticholinergics, amantadine, and dopamine agonists, MAO inhibitors, and lastly, levodopa, after ruling out any treatable or reversible exacerbating factors (Armstrong & Okun, 2020). According to the International Parkinson and Movement Disorder Society, clozapine would be the drug of choice for treatment of psychosis in PD (Seppi et al., 2018), although regular blood draws to assess for iatrogenic agranulocytosis make this a cumbersome choice for patients. Quetiapine is the most widely used antipsychotic for PD-related psychosis, in conjunction with clozapine (Goldman & Holden, 2014), as it has less D2 antagonism than many other atypical or second generation antipsychotics. Pimavanserin, a selective inverse serotonin 5-HT2A receptor agonist, is the only FDA-approved drug for psychosis in PD (Cummings et al., 2014). PD-associated sleep disorders are not uncommon and should be thoroughly evaluated. The RECOVER trial has supported the efficacy of rotigotine in improving nocturnal sleep disturbances and night-time disabilities such as limb restlessness, immobility, pain, and cramps (Trenkwalder et al., 2011). Continuous positive airway pressure is effective for obstructive sleep apnea (Seppi et al., 2018). REM sleep behavior disorder, a common problem in patients with PD often present decades prior to the onset of motor symptoms, can be treated with melatonin and, if not effective, clonazepam can be used, however, more evidence is needed for validation of these medications (GBD 2016 Parkinson's Disease Collaborators, 2018).

Finally, autonomic dysfunction often occurs in patients with PD. It has been suggested that fludrocortisone, midodrine, and short-term droxidopa are effective for the treatment of neurogenic orthostatic hypotension. For sexual dysfunction in male PD patients, sildenafil is an effective option to treat erectile dysfunction with acceptable risk profile and no specialized monitoring. Probiotics and prebiotic fiber can be used for the treatment of constipation. Mosapride, a selective 5-HT4 receptor agonist, has shown to be improve colorectal motility in patients with PD (Liu et al., 2005). Macrogol, an osmotic laxative, and lubiprostone, a chloride channel activator, have also been studied for constipation in PD with positive results, although additional research is encouraged to better determine their efficacy (Pedrosa Carrasco, Timmermann, & Pedrosa, 2018). Botulinum toxin injections are efficacious and clinically useful for the management of sialorrhea; glycopyrrolate can also be used, however, should be used with caution given the potential side effects (Armstrong & Okun, 2020; Seppi et al., 2018). As mentioned earlier, apomorphine might be effective for the treatment of nonmotor features such as hyperhidrosis, urinary symptoms, and fatigue (Martinez-Martin et al., 2011).

FUTURE PERSPECTIVES

Research for newer therapies in PD is ongoing and several studies have shown promising results. Pharmacotherapy helps mitigate motor symptoms, however search for an effective therapeutic target is underway to help with disease-modifying pharmacotherapies and/or neuroprotective agents. Despite the central role α-synuclein plays in PD pathology, complete suppression of the protein appears to be detrimental. Thus, current strategies are

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aiming to merely reduce levels of α-synuclein instead. Prasinezumab, a humanized monoclonal antibody that targets the C-terminus of aggregated α-synuclein, has been shown to reduce free serum concentrations of the protein by 97% (Jankovic et al., 2018; Stoker & Barker, 2020). Nevertheless, preliminary results available in ClinicalTrials.gov (NCT03100149) did not show superiority compared to placebo regarding motor and non-motor functions in patients with PD. Another molecule targeting the N-terminal portion of α-synuclein has resulted in improvement of the motor phenotype in a PD mouse model, and has also been found to be well-tolerated in humans (Brys et al., 2019).

Regarding novel applications of DBS, targeting the pedunculopontine nucleus has been considered for the treatment of PD. However, evidence for this indication was inconclusive, which may be attributed to suboptimal programming settings, low sample sizes, and the anatomical variability of this structure in the human brain (Stoker & Barker, 2020). Stimulation of the substantia nigra pars reticularis may be helpful in reducing axial symptoms (Weiss et al., 2013)advanced programming with interleaved pulses was put forward to introduce concomittant nigral stimulation on caudal contacts of a subthalamic lead. Here, we hypothesized that the combined stimulation of subthalamic nucleus and substantia nigra pars reticulata improves axial symptoms compared with standard subthalamic nucleus stimulation. Twelve patients were enrolled in this 2 × 2 cross-over double-blind randomized controlled clinical trial and both the safety and efficacy of combined subthalamic nucleus and substantia nigra pars reticulata stimulation were evaluated compared with standard subthalamic nucleus stimulation. The primary outcome measure was the change of a broad-scaled cumulative axial Unified Parkinson's Disease Rating Scale score (Scale II items 13-15, Scale III items 27-31, and thoracic spinal cord stimulation might decrease freezing episodes in patients with advanced PD (Samotus, Parrent, & Jog, 2018).

Evidence is still lacking to support the use of creatine, coenzyme Q-10, vitamin E, and other therapies as neuroprotective strategies in patients with PD (Rizek, P. Kumar, N. Mandar, 2016). Several clinical trials are underway which expand upon established research and animal-based studies regarding cellular based therapies for PD such as mesencephalic fetal cell transplantation, mesenchymal stem cell therapy and induced pluripotent cells. However, evidence is still lacking on the exact role of cellular based therapies in the treatment spectrum of PD (Elkouzi, Vedam-Mai, Eisinger, & Okun, 2019).

PD is a multifaceted, heterogeneous disease with effective pharmacologic, nonpharmacologic and surgical symptomatic therapy. Continued efforts are underway to enhance symptomatic treatments that mimic the physiologic release of dopamine in addition to identifying an effective disease modifying therapy.

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Use of Cannabidiol in Movement Disorders – A Brief Review

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INTRODUCTION

Movement disorders constitute a major category of neurological diseases that impose a heavy toll on affected individuals (Wenning et al., 2005). While many of these diseases - including Parkinson's disease (PD), Huntington's disease (HD), and dystonia - lack curative or disease-modifying therapies, their symptomatic burden can be reduced with a diverse array of treatments currently available (Albanese, Di Giovanni, & Lalli, 2019; Mao, Qin, Zhang, & Ye, 2020; McColgan & Tabrizi, 2018). Despite progress in the management of movement disorders over the preceding decades, newer therapies have the opportunity to further improve the standard of care.

Among the list of potentially novel treatments, cannabidiol (CBD) - one of the many phytocannabinoids found in the plant *Cannabis sativa* - has emerged as a promising candidate for use in a variety of neurological and neuropsychiatric diseases (Fernández-Ruiz et al., 2013; Premoli et al., 2019). Indeed, CBD has been described as an anxiolytic, antipsychotic, antidepressant, and antiepileptic, making it potentially applicable to a wide range of symptoms that are present in movement disorders (McPartland, Duncan, Di Marzo, & Pertwee, 2015; Peres et al., 2018). Additionally, the hypokentic effects of cannabinoids may be translated into therapies for certain hyperkinetic movement disorders (Lastres-Becker et al., 2002; Peres et al., 2018). In this brief report, we will review the pharmacology of CBD, as well as the clinical evidence underlying its potential usefulness as a therapy for a number of movement disorders.

MOLECULAR MECHANISMS OF CBD

The mechanism of action of CBD is complex and incompletely understood (McPartland et al., 2015). Like Δ9-tetrahydrocannabinol (Δ9-THC), the psychoactive compound that makes marijuana a popular recreational drug, CBD also interacts with the G protein-coupled receptors (GPCRs) that comprise the endocannabinoid system, albeit in a different manner (Peres et al., 2018). Whereas Δ9-THC is a partial agonist of both CB1 and CB2 (Mechoulam, Fride, & Di Marzo, 1998), CBD is thought to counter this effect by acting as an inverse agonist of CB1 and CB2 (Pertwee, 2008), as well as exerting negative allosteric modulation of both receptors (Laprairie, Bagher, Kelly, & Denovan-Wright, 2015; Martínez-Pinilla et al., 2017). CBD also modulates the endocannabinoid system by preventing the breakdown and uptake of amantadine, the primary endogenous cannabinoid (Bisogno et al., 2001; Pertwee & Ross, 2002). In addition to the classical endocannabinoid receptors, CBD also interacts with multiple targets within the "expanded endocannabinoid system", including several of the Ca2+-permeable transient receptor potential (TRP) channels (e.g., TRPV1, TRPA1, and TRPM8), suggesting involvement of the cannabinoid in Ca2+ signaling (McPartland et al., 2015; Venkatachalam & Montell, 2007). Thus, CBD influences the endocannabionoid system in unique manner, which is dissimilar – and in some ways, opposite – to the pharmacolgical effects of Δ9-THC. This distincation is important to emphanize when considering cannabinoids for clinial use since the side effect profile of certain agents may be undesierable. A major difference in this regard is the apparent absence of intoxicating or psychotomimetic effects with CBD, which is not true for Δ9-THC (Englund, Freeman, Murray, & McGuire, 2017; Morgan et al., 2018). Indeed, there is evdience that CBD has antipsychotic properties (Englund et al., 2013; Leweke et al., 2012). Thus, CBD influences the endocannabinoid system in unique manner, which is dissimilar – and in some ways, opposite – to the pharmacological effects of Δ9-THC. This distinction is important to emphasize when considering cannabinoids for clinical use since the side effect profile of certain agents may be undesirable. A major difference in this regard is the apparent absence of intoxicating or psychotomimetic effects with CBD, which is not true for Δ9-THC (Englund et al., 2017; Morgan et al., 2018). Indeed, there is evidence that CBD has antipsychotic properties (Englund et al., 2013; Leweke et al., 2012).

Of note, CBD is a relatively undiscriminating ligand, interacting with multiple targets outside of the endocannabinoid system (McPartland et al., 2015; Peres et al., 2018). With respect to neurotransmission, the compound directly influences the serotonergic and dopaminergic systems by acting as a low-affinity agonist of the 5-HT_{1A} receptor and a partial agonist of the D_2 receptor, respectively, which may account for some of its neuropsychiatric effects (Gomes, Resstel, & Guimarães, 2011; Seeman, 2016). CBD also indirectly enhances activity of adenosine A_{2A} receptors by increasing levels of adenosine via uptake inhibition (Liou et al., 2008)a nonpsychotropic, nontoxic compound has been shown to block diabetes- and endotoxin-induced retinal damage. Howev-

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er, the protective mechanism of this anti-inflammatory cannabinoid is not completely understood. The goal of this study is to determine the role of adenosine signaling in retinal inflammation and its potential modulation by CBD. METHODS. The adenosine receptor (AR. Moreover, various studies have provided evidence that CBD allosterically modulates GABAergic, glycinergic, and opioid receptors, further demonstrating the promiscuity of the molecule (Bakas et al., 2017; Kathmann, Flau, Redmer, Tränkle, & Schlicker, 2006; Mchugh et al., 2010; McPartland et al., 2015).

The anti-inflammatory and antioxidant effects of CBD are likely mediated by a litany of mechanisms including modulation of the arachidonic acid pathway, reduction in nitrous oxide generation, inhibition of cytokines, and ability to lower reactive oxygen species, amongst others (Atalay, Jarocka-karpowicz, & Skrzydlewskas, 2020; McPartland et al., 2015). Additionally, CBD is known to participate in nuclear signaling, as it binds to and transcriptionally activates PPARγ, which may also play a role in its anti-inflammatory properties (O'Sullivan, 2016). CBD also affects intracellular ionic concentrations by diminishing the activity of both voltage-gated Ca^{2+} channels and voltage-gated Na^{+} channels, which likely contribute to its antiepileptic effects (Ghovanloo et al., 2019).

CBD IN PARKINSON'S DISEASE

PD is the most prevalent movement disorder and the second most common neurodegenerative disease after Alzheimer's disease, affecting 1-3% of people over the age of 65, with approximately 1 million individuals affected in the United States alone (Marras et al., 2018; Raza, Anjum, & Shakeel, 2019). The underlying pathophysiology of the disease is characterized by progressive degeneration of dopaminergic neurons located in the substantia nigra pars compacta alongside the accumulation of Lewy bodies - cytoplasmic inclusions of aggregated α-synuclein. These cellular changes are accompanied by the classical clinical manifestations of bradykinesia, resting tremor, rigidity, and postural instability. Other common symptoms present in PD include constipation, olfactory decline, sleep disruption (e.g., REM behavior sleep disorder), autonomic dysfunction, and dementia (Sveinbjornsdottir, 2016). Furthermore, individuals with PD may be affected with a range of neuropsychiatric symptoms such as anxiety, depression, apathy, and psychosis (Mueller et al., 2018).

The cardinal symptoms of PD are clinically managed by utilizing various pharmacological (e.g., exogenous dopamine precursor supplementation, D2 receptor agonist treatment, and inhibition of dopamine breakdown) and surgical strategies (e.g., deep brain stimulation of nuclei that modulate the direct/indirect pathway in the basal ganglia) that compensate for loss of dopaminergic neurons (Raza et al., 2019). Additionally, non-motor symptoms are treated with medications that reflect the particular symptoms a given individual with PD may be experiencing, such as SSRIs for anxiety and depression or polyethylene glycol for constipation (Mueller et al., 2018; Rossi, Merello, & Perez-Lloret, 2015).

The literature addressing whether or not CBD should be utilized in the treatment of PD is somewhat limited, but there are indications it may be useful, especially for neuropsychiatric symptoms (Buhmann, Mainka, Ebersbach, & Gandor, 2019; Peres et al., 2018). One of the first randomized controlled trials (RCTs) that involved CBD was conducted in 2004, and administered whole plant extract (THC-to-CBD ratio was defined as 2:1) to PD patients (n = 17). No significant improvement of motor symptoms was evidenced in this report (Carroll et al., 2004). Later a RCT with daily doses of CBD (n = 21; subjects received either placebo, 75 mg, or 300 mg) observed a significant improvement in PDQ-39 scores, which measures quality of life in PD, in the high-dose treatment arm. Again, no difference was found with respect to motor symptoms (Chagas, Zuardi, et al., 2014). While not a RCT, a small open-label pilot study (n = 6) evaluated the use of CBD in PD patients with psychosis, finding that a daily 150 mg dose taken for one month improved scores on multiple psychiatric rating scales (Zuardi et al., 2009). Furthermore, a case series (n = 4) found that CBD (either 75 mg or 300 mg doses) mitigated PD-associated REM behavior sleep disorder symptoms (Chagas, Eckeli, et al., 2014).

Altogether, the clinical evidence obtained to date suggests CBD may be an effective therapy for neuropsychiatric symptoms in PD, including psychosis and sleep disturbances (Chagas, Eckeli, et al., 2014; Zuardi et al., 2009). Furthermore, CBD therapy improved a measure of overall quality of life in PD patients, possibly demonstrating its anxiolytic and antidepressant effects (Chagas, Zuardi, et al., 2014). However, it is important to note that much of the evidence available so far has not come from RCTs, and more rigorous studies are warranted. Of note, RCTs have been conducted evaluating other cannabinoids - namely, nabilone and rimonabant - in the treatment of PD-associated motor symptoms, but the results are mixed, warranting additional investigation into the potential benefit of these compounds as well (Buhmann et al., 2019).

CBD IN HUNTINGTON'S DISEASE

HD is an inherited neurodegenerative disease caused by the expansion of a trinucleotide repeat (CAG) in the first exon of the huntingtin gene. Clinically, the disease is characterized by a triad of hyperkinetic motor symptoms, cognitive decline, and neuropsychiatric disorders, thought to be driven by toxic accumulation of mutant huntingtin protein in the striatum and neocortex (McColgan & Tabrizi, 2018). Much less common than PD, the worldwide prevalence of HD is estimated to be 2.71 per 100,000 (Pringsheim et al., 2012). There are no disease-modifying therapies available for HD, and clinical management of the disease is primarily directed towards symptomatic relief. Chorea, the dominant motor manifestation of HD, is typically treated with VMAT2 inhibitors and antipsychotics, which are dopamine-depleting and dopamine blocking agents, respectively (Coppen & Roos, 2017).

Given the purported ability of cannabinoids, including CBD, to induce hypokinetic effects, there has been considerable interest in evaluating their use in HD to treat chorea (Lastres-Becker et al., 2002; Peres et al., 2018). In fact, an early RCT (n = 15; crossover design) administered daily doses of CBD (~700 mg) for six weeks to evaluate HD-associated chorea. Despite being well tolerated, no significant improvement in chorea

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or any secondary outcomes was found (Consroe et al., 1991). More recently, a cannabinoid combination (i.e., ^{9}-THC/CBD mixed in 1:1 ratio) has been used in a number of HD-related preclinical and human studies (Peres et al., 2018). Despite promising reports in animal models of HD showing neuroprotective effects of the ^{9}-THC/CBD combination (Sagredo et al., 2011; Valdeolivas, Sagredo, Delgado, Pozo, & Fernández-Ruiz, 2017)which are the main constituents of the cannabis-based medicine Sativex, provide neuroprotection in rat models of Huntington's disease (HD, a subsequent human RCT (n = 24; crossover design) using nabiximols, an oromucosal spray formulation that contains the ^{9}-THC/CBD ratio used in the preclinical studies, found no difference in motor, behavioral, cognitive, or functional measures when compared to placebo (López-Sendón Moreno et al., 2016)stimulation of specific targets within this signaling system has been investigated as a promising therapeutic agent in HD. We conducted a double-blind, randomized, placebo-controlled, cross-over pilot clinical trial with Sativex®, a botanical extract with an equimolecular combination of delta-9-tetrahydrocannabinol and cannabidiol. Both Sativex® and placebo were dispensed as an oral spray, to be administered up to 12 sprays/day for 12 weeks. The primary objective was safety, assessed by the absence of more severe adverse events (SAE. In contrast, a case series (n = 7) found that treatment with a variety of cannabinoids (i.e., either dronabinol, nabilone, or nabiximols) led to a significant improvement in the UHDRS, specifically due to marked improvement in the dystonia subscore. Reduction in irritability and apathy was also observed. However, given that only two of the seven subjects received nabiximols, any inferences from this study are limited (Saft et al., 2018).

Overall, the evidence supporting the use of CBD in HD is currently lacking, demonstrating the need of larger and more rigorous studies. While the effectiveness of CBD in treating symptoms such as chorea and dystonia is still an open question, effort should also be directed towards the potential benefits CBD may have with respect to the neuropsychiatric symptoms of HD (Peres et al., 2018). As with PD, the anxiolytic, antidepressant, and antipsychotic properties of CBD may be especially well suited to treat the non-motor manifestations of HD. Lastly, studies have been conducted that evaluated the efficacy of other species of cannabinoid, such as nabilone (Curtis, Mitchell, Patel, Ives, & Rickards, 2009). These studies have produced mixed results and, like with CBD, more evidence is needed (Peres et al., 2018).

CBD IN DYSTONIA AND SPASTICITY

A few studies on the effect of CBD in primary dystonia and spasticity have been conducted (Peres et al., 2018). Dystonia is a hyperkinetic movement disorder characterized by sustained and involuntary muscle contractions that induce repetitive, twisting movements and atypical posture. While secondary dystonia is triggered by an underlying cause or condition, primary dystonia, which is the most common category, typically has a genetic basis (Phukan, Albanese, Gasser, & Warner, 2011). In the 1980s, a small (n = 5) study evaluated the use of CBD (maximum daily dose of 600 mg) in a series of dystonic patients and found a 20-50% reduction in dystonia over a six-week period. Interestingly, this improvement was observed in both primary and secondary dystonias (Consroe, Sandyk, & Snider, 1986). A case series from the same period corroborated these findings in two subjects who experienced fast-acting (i.e., less than 24 hours) and marked improvement in their chronic dystonic symptoms after a single 200 mg dose of CBD (Sandyk, Snider, Consroe, & Elias, 1986). While these small reports are intriguing, future RCTs are needed to validate these findings.

Spasticity is a sign of pathology in upper motor neurons, and is often associated with a primary condition, such as stroke, multiple sclerosis (MS), or cerebral palsy (Rekand, 2010). Clinically, spasticity is characterized by a velocity-dependent increase in muscle tone, muscle stiffness, and sustained contraction. This limits functionality of affected body parts and causes pain, markedly impairing quality of life (Chang et al., 2013). The effect of CBD on spasticity has primarily been studied in the context of MS, with a number of studies suggesting that nabiximols reduces the severity of spasms, is well tolerated, and improves quality of life for afflicted individuals (Giacoppo, Bramanti, & Mazzon, 2017). Indeed, relative to the movement disorders previously discussed, the use of CBD for MS-associated spasticity has been more extensively investigated, with no fewer than five RTCs conducted over the past 20 years testing the efficacy of nabiximols (C. Collin, Davies, Mutiboko, & Ratcliffe, 2007; Christine Collin et al., 2010; Novotna et al., 2011; Vachová, Novotná, & Mares, 2013; Wade, Makela, Robson, House, & Batemen, 2004). While generally encouraging, as with other studies evaluating nabiximols, the effect of CBD alone on spasticity cannot be disentangled from the effect of CBD and Δ9-THC administered together without further investigation.

CONCLUSION

Despite the growing popularity of CBD as a 'panacea' for a wide range of symptoms and conditions, there is currently a lack of reliable clinical evidence to support the efficacy of this compound, as well as other cannabinoids, for many of these conditions, including movement disorders (Kluger, Triolo, Jones, & Jankovic, 2015). Of the studies that have been conducted for PD, HD, dystonia, and spasticity, only a minority are RCTs, and many of them evaluate the effect of CBD in combination with ^{9}-THC. Given the complex pharmacological interplay that the prominent phytocannabinoids exhibit, definitive answers regarding the therapeutic potential of these compounds will only be obtained once larger and more rigorous RCTs are conducted that evaluate the efficacy of each cannabinoid separately, as well as in combination, for specific conditions (Kluger et al., 2015; McPartland et al., 2015).

Among the available evidence, studies supporting the use of CBD to treat neuropsychiatric symptoms associated with specific movement disorders are particularly intriguing. More effort, mainly through appropirately powered RCTs, should be directed towards expeditiously answering whether or not CBD can be utilized to mitigate these particularly disruptive symptoms, which are common in several different movement disorders.

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Apentosis

David B. Rosenfield, M.D.

It is fairly pointless to give someone a nice pen as a present. We all increasingly use pens less and less, except for the diehard pen aficionados who collect them. For me, most of my direct input to patients' charts is performed on a computer. And, I personally seldom write anything, except thank-you notes or sympathy cards.

Further, I cannot possess an expensive pen for any significant length of time. I don't know whether I leave them on desks, someone takes them or they disappear on their own. For whatever reason, they disappear and remain gone.

Within this context of disappearing pens, I recently noticed that, especially regarding the inexpensive disposable writing instruments, they seem to have a life form of their own: they disappear and reappear over multiple times and are found in multiple locations, all independently and on their own.

Louis Pasteur at one time queried whether infectious agents might be life forms that emerged spontaneously in milk or in wine (or disease). He subsequently discerned that they were not and developed a system of pasteurization which safeguarded milk and also saved the French wine industry.

Similarly, getting back to pens, I sometimes query whether a pen that spontaneously appears in my suit, white coat, pants or anywhere else might be its own spontaneous life form ala Pasteur and, just as easily as it can appear, can cease to exist and be gone.

Some of us physicians might ponder whether we need pens anyway: they certainly don't own truth finding mechanisms which provide exigencies in health care. Indeed, many of us are aware that several educational systems have removed one of pens' products (e.g., writing script) from the educational matrix, a perspective with which many children agree: What do you need a pen for anyway, let alone writing script, when you can use your portable social media device?

Maybe, one day in the future, people will look at writing, the actual act of writing, as something they can view in a café. If so, where "goest" the pen?

Maybe, it's sort of like fire. Think about it: 100 years from now, people may visit a cafe and look at a display of fire. The pamphlet the café hands out might state, "Before microwaves and various electronic heating devices, they had a thing called fire. Due to environmental concerns, people gradually eliminated fireplaces from homes and, as time went on, with cessation of smoking and its accouterments of matches and lighters, we no longer have fire. But, if you want to know what fire looks like, this is what it is. Come on in. By the way, don't touch it."

Imagine: people get out of their Tesla, grab their Starbucks coffee and enter some place to watch a thing called Fire. Maybe the café will even have some pens on display.

Putting aside that we are losing different parts of society, be it pens, fire, vocational positions such as travel agents or porters at airports, 45 rpm vinyl disks, eight-track cartridge tapes, abacuses, slide rules or physicians in training being on call every other night so that they are not too tired, we are witnessing a changing world, one that includes disappearance of pens, possibly fire and who knows what else to come.

Could one argue that this is a different form of apoptosis (e.g., programmed death of cells) which affects us all? Pasteur, in his development of germ theory of disease, surely kept his pen and pencil at his side, given the lack of other electronic writing utensils.(Maybe he could help me figure out where my pens are).

I was once on a tour in Paris and the guide asked our group who was the most famous Frenchman. For whatever reason, she called on me. I replied, "Pasteur." The guide smiled and said, "No.".So,I then posited Victor Hugo and,again,she replied in the negative, informing me and the others the correct answer: Napoleon.

"But," I said, "He lost."That was when I learned that people may be remembered more for what they did rather than for what they didn't. Regardless, I'm fairly certain that Napoleon Bonaparte as well as Louis Pasteur had pens at the ready, as certainly did Victor Hugo.

But, if people can be remembered more for what they did and not for what they didn't, perhaps my pens, wherever they are, might be remembered more for what they wrote rather for what they did not. The competency of the instrument was there, all that was lacking was appropriate associated cerebral activity.

Perhaps if I started collecting pens, they might exercise a reverse cerebration upon my being. Or, perhaps not.

Marcel Proust, Anton Chekhov, Leo Tolstoy and W. H. Auden, not to mention others, failed to win the Nobel Prize in literature. Yet, we all know these are great writers. Perhaps, they had the wrong pen.

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Combined central and peripheral demyelination syndrome after first Pfizer SARS-COVID-19 mRNA vaccine with brisk response to plasma exchange and steroids

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KEY WORDS:
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INTRODUCTION:

In the midst of the world-wide SARS-COVID19 pandemic, several vaccines have been granted emergency authorization status by the US Food and Drug Administration (FDA) after early trials demonstrated satisfactory safety and effectiveness data. Combined central and peripheral demyelination (CCPD) is a rare, immune-mediated disorder that involves demyelination of the central and peripheral nervous systems. In this manuscript, we present a patient who developed CCPD 22 days after receiving her Pfizer mRNA SARS-COVID-19 vaccine and describe an intervention that provided a good outcome. We also provide a clinically relevant literature summary on this uncommon clinical entity. To our knowledge, this is the first report of such a complication after administration of the Pfizer SARS-COVID mRNA vaccine.

CASE DESCRIPTION:

A 59-year-old female with past medical history of Hashimoto's Thyroiditis was admitted to a large military hospital after a 3-day history of progressive lower extremity pain, weakness and urinary incontinence. The patient's history did not reveal evidence of recent acute illness and was significant for receiving her Pfizer SARS-COVID-19 mRNA vaccine 22 days prior to presentation. She had a maternal aunt with Multiple Sclerosis and also had underwent a recent bunion surgery at an outside hospital. Neurologic exam on presentation was notable for mild somnolence but otherwise unremarkable mental status exam. She had restricted right lateral gaze with horizontal end-gaze nystagmus, right eye red desaturation without afferent pupillary defect, ocular ataxia, and left lower facial weakness. She demonstrated right upper extremity weakness and dysmetria in addition to bilateral upper extremity hyperreflexia. In the lower extremities, she had a dense and symmetric paraparesis with decreased reflexes and numbness. Additionally, she demonstrated overflow incontinence likely secondary to bladder atonia.

MRI of the brain and spinal cord showed multifocal supratentorial, infratentorial, cervical and thoracic cord white matter signal abnormalities with trace enhancement in combination with marked cauda equina enhancement.

The patient was diagnosed with CCPD. She was treated with 1 gram IV methylprednisolone daily for five days concomitant with five treatments of plasma exchange spaced every other day. At time of discharge, the patient's exam showed improvement of her mental status and resolution of her ocular findings. Her lower extremity strength had improved, though she continued to have decreased reflexes and sensation. Repeat imaging demonstrated stability of her supratentorial and infratentorial white matter abnormalities with resolution of the associated contrast enhancement. There was persistent nerve root enhancement associated with her spinal imaging. She was discharged to acute rehab with a 2-week prednisone taper.

At a follow-up appointment in the clinic one month after initial presentation, that patient exhibited marked improvement. She was able to ambulate independently, though used a walker for balance, and had near full return of her lower extremity strength. Her primary residual symptom was neuropathic pain that responded well to gabapentin. After extensive discussion, the patient elected not to start disease modifying therapy given the uncertain and possibly monophasic course of her disease. At time of this article, the patient was pending repeat nerve conduction studies and imaging.

DISCUSSION:

Neuroimmunologic conditions causing demyelination in either the central nervous system (i.e. multiple sclerosis (MS), etc.) or the peripheral nervous system (i.e. chronic inflammatory demyelinating polyradiculoneuropathy (CIPD), etc.) are commonly encountered in clinic practice. Combined central peripheral demyelination syndrome (CCPD) is a term coined to describe syndromes with simultaneous or sequential demyelination in both the peripheral and central nervous system.[1] CCPD is an uncommon condition and only case reports and small case series are available to guide clinical management. One case series of 31 patients from two medical centers in Europe described CCPD clinical features to include lower limb sensorimotor symptoms (n=29, 94%), urinary incontinence/retention (n=26, 84%), distal sensory changes (n=11, 35%) and upper limb sensorimotor impairment (n=8, 26%) among others.[2] The mean age of presentation was 57 years old, but there was a large range (14-82 years old), and the condition was more commonly seen in males (n=23, 74%). More than half of patients had a proceeding infection (n=20, 65%) and the clinical course was heterogeneous

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Fig 1: FLAIR and T1-weighted post-contrast images of the brain demonstrate confluent areas of increased FLAIR white matter signal hyperintensity involving the subcortical, deep and periventricular regions. There are additional areas involving the bifrontal white matter (Fig 1A and D), splenium (Fig 1B and E) and brachium pontis bilaterally (Fig 1C and F) which show areas of enhancement.

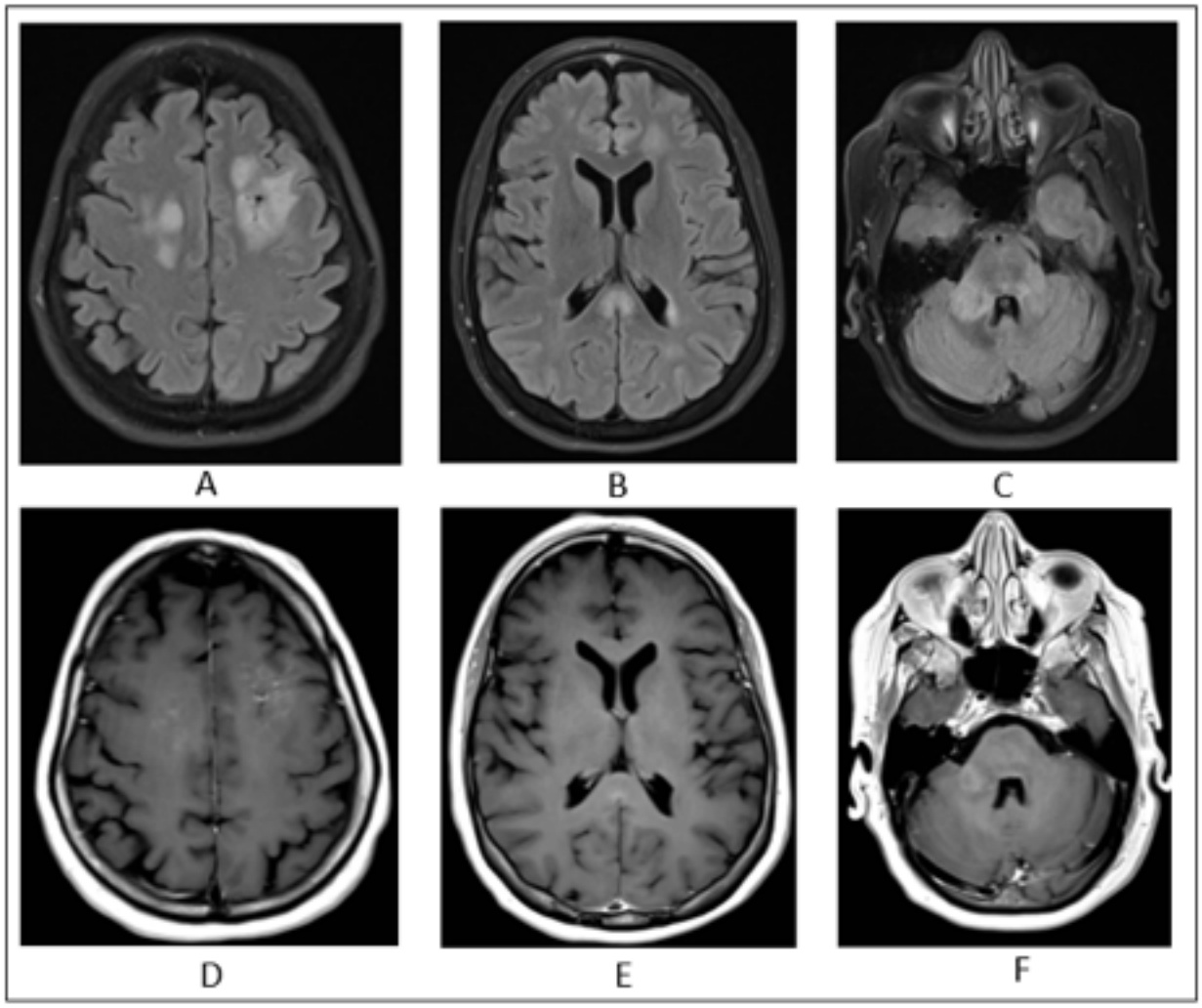

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Fig 2: Sagittal and axial T2-weighted imaging of the cervical spine (Fig 2A and B) reveal an area of T2 signal abnormality predominantly involving the central aspect of the cord extending from the cervicomedullary junction to C2-3. Representative axial pre- (Fig2C) and post-contrast (Fig2D) T1-weighted imaging of the cervical spine demonstrate enhancement of ventral roots. Axial T1-weighted pre (Fig2E) and post-contrast (Fig2F) weighted imaging and sagittal T1-weighted fat-suppressed post-contrast imaging (Fig2G) shows intense enhancement of nerve roots of the cauda equina.

SARS-COVID-19 PCR was negative on admission and on re-testing two days after admission. CSF studies showed albumino-cytologic dissociation (protein of 184 and 2 nucleated cells). Serum labs were notable for elevated anti-TPO antibodies (stable from prior visits/encounters) and elevated VEGF. West Nile IgM/IgG, Anti-MOG, Anti-Aquaporin-4, neurofascin-155 and contactin-1 antibodies were negative. There were no oligoclonal bands. Motor nerve conduction studies were consistent with an acute acquired demyelinating polyneuropathy. Electromyography (EMG) and sensory studies were unremarkable.

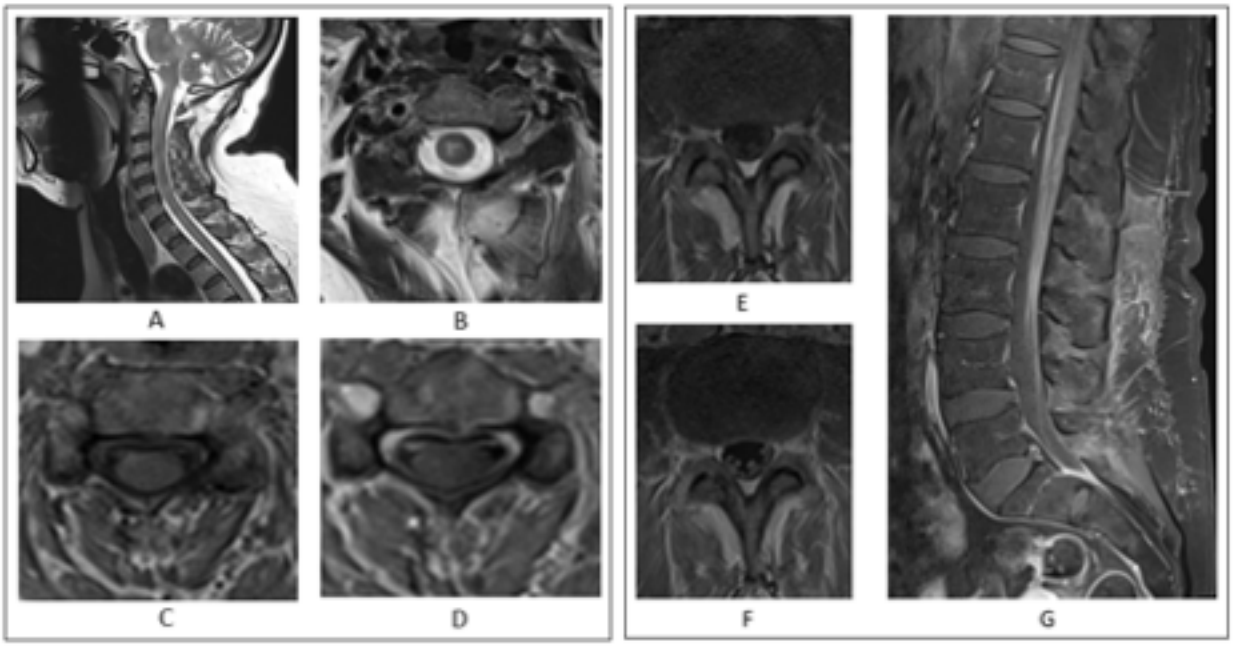

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Fig 3: Laboratory and Nerve Conduction/Electromyography Data

CSF Protein: **184** mg/dL	CSF Nuc Cells: 6 cells/mcL	RFP: unremarkable
CSF Glucose: 54 mg/dL	CSF RBCs: 1 cells/mcL	CBC: unremarkable
COVID19 PCR: negative	Acute Hepatitis: negative	HFP: unremarkable
Syphilis Screen: negative	HIV Screen: negative	Chronic Hepatitis: negative
MOG Ab: negative	VEGF: **194** (<115) pg/mL	Copper: **220** (<165) mcg/dL
Aquaporin-4 Ab: negative	GAD65 Ab: <5 U/mL	Zinc: 82 mcg/dL
ACE: 2.6 U/L	Insulin Ab: <5 mcU/mL	Vitamin B12: 665 pg/mL
Oligoclonal Bands: 0	Islet Cell 512 Ab: **60** (<7.5) U/mL	Nuclear Ab: negative
Adenosine Deaminase: 1 U/L	Thyroglobulin Ab: 2.6 IU/mL	TSH: 1.3 mcIU/mL
CSF Cytology : unremarkable	TPO Ab: **30.78** (<5.6) IU/mL	UDS: unremarkable
IgM/IgG GMI: negative	IgM MAG: negative	IgM GD1a: negative
IgM GalNAc-GD-1a: negative	IgM Histone H3: negative	IgM/IgG Beta-Tubulin: negative
IgG neurofascin-140: negative	IgM/IgG neurofascin-155: negative	IgG contactin-1: negative

MOTOR NERVE CONDUCTION SUDY	Site	Distal Latency (ms)	Amplitude (mV)	Conduction Velocity (m/s)
Left Peroneal (EDB)	Ankle	**NR**	**NR**	
	Fibular Head	**NR**	**NR**	
Left Tibial	Ankle	**7.5**	3.6	
	Popliteal Fossa	12.1	3.1	49
Left Peroneal (TA)	Fibular Head	2.9	2.6	
	Popliteal Fossa	5.1	2.7	**32**
Right Peroneal	Ankle	6.6	**0.5**	
	Fibular Head	13.8	**0.4**	42
	Popliteal Fossa	15.4	**0.4**	47
Right Tibial	Ankle	**8.1**	5.1	
	Popliteal Fossa	16.0	**1.1**	44
Left Median	Wrist	**4.8**	5.5	
	Elbow	8.8	5.3	54
Left Ulnar	Wrist	**4.4**	**4.8**	
	Below Elbow	8.8	5.0	**46**
	Above Elbow	11.6	**4.2**	**36**

F-WAVE STUDIES	M Latency (ms)	F Latency (ms)
Left Tibial	8.8	52.5
Right Perioneal	6.7	**NR**
Right Tibial	8.8	**69.3**
Left Median	5.0	**38.0**
Left Ulnar	4.7	**40.7**

SENSORY NERVE CONDUCTION STUDY	Site	Peak Latency (ms)	Amp (μV)	Distance (mm)	Conduction Velocity (m/s)
Left Superficial Peroneal	Lower leg	2.6	12	100	56
Right Superficial Peroneal	Lower leg	2.5	13	100	68
Left Radial	Forearm	2.0	63	100	67
Left Median	Wrist (median)	3.5	18	130	52
Left Ulnar	Wrist (Ulnar)	2.5	14	110	61

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(monophasic: n=10, 32%; relapsing: n=13, 42%, chronic progressive: n=8, 26%). Treatment was variable, but most patients responded to treatment (steroids: 17/23, 74%; IVIG: 4/8, 50%; other: 1/1, 100%). The characteristics described in another large case series of 40 patients in Japan had some differences.[3] The mean age on onset was younger (31.7 years old) and there were more female patients than male (male: n= 11; female: n=29). There was a similar distribution of clinical course (monophasic: n=10, 26.3%; relapsing: n=20, 52.6%, chronic progressive: n=8, 21.1%) and patients had similar but heterogeneous symptoms (motor weakness: 37/40, 92.5%; sensory disturbances: 37/39, 94.9%). Most in this cohort also improved with treatment (steroids: 30/36, 83.3%; IVIG 18/27, 75%; plasmapheresis: 7/8, 87.5%; IFN-beta: 1/10, 10%) but a certain proportion still went on to develop a chronic or relapsing disease. A smaller case series of patients in China (n=22; M/F: 11/11) showed similar presenting symptoms but were more likely to have a monophasic rather than relapsing or chronic course (monophasic: n=15/22, 68.1; relapsing: n=3, 18.1%, chronic progressive: n=4/22, 27.2%).[4]

Definitive diagnostic criteria has yet to be established, but we used the definition set forth by Otaga and colleagues[3] to include: (1) CNS involvement criterion: T2 high-signal intensity lesions in the brain, optic nerves, or spinal cord upon MRI, or abnormalities on visual-evoked potentials (VEPs). (2) PNS involvement criterion: conduction delay, conduction block, temporal dispersion or F-wave abnormalities, suggesting peripheral demyelinating neuropathy according to nerve conduction studies (NCS).[3]

The pathophysiology of CCPD remains uncertain and is potentially multifactorial.[5] Proposed theories include independently occurring disease, a common immunogenic target in both the CNS and PNS, or a complication of treatment for another autoimmune condition.[5,6] Several elevated antibody titers have been seen in patients with CCPD including anti-MOG antibody,[7,8] Aquaporin-4 antibodies,[9] and others.[3] Antibody titers against Neurofascin-155, an antigen found in the CNS and PNS[10], have been elevated in a proportion of patients with CCPD and has been proposed to be a unifying link.[3,10] This antibody has also been seen in a minority of patients with MS and CIDP but is not ubiquitous, suggesting that the pathophysiology may be more complicated.[11] Further research must be done to better understand this illusive clinical entity.

Preferred treatment has yet to be determined[2] and some medications, such as interferon-beta have been shown to worsen a patient's course.[3,10] Acute treatments including steroids, IVIG and plasmapheresis have shown benefit in a proportion of patients, though predicting a patient's course remains challenging.[2,3] Chronic immune therapies to include Rituximab and Natalizumab have shown to be somewhat effective in a few patients with relapsing disease.[12]

Acute central or peripheral demyelination appears to have a very uncommon association to the SARS-COVID19 vaccine. Early vaccine safety data were reassuring[12], but a clearer understanding will likely come amidst the world-wide vaccination effort. Of 704,003 patients who received their first dose of the Pfizer SARS-COVID19 mRNA vaccine in Mexico, there were only three cases of Guillain-Barré Syndrome (GBS) (0.43/100,000 doses) and two cases of acute transverse myelitis (TM) (0.28/100,000 doses).[13] Potential future instances of these complications and our understanding of the risks will likely evolve over time.

As with any temporally related complication, it is not possible to say whether the CCPD syndrome in our patient was definitively from the SARS-COVID-19 mRNA vaccine. The patient did have evidence of co-autoimmunity (elevated anti-TPO antibodies), which may have been a risk factor. Elevated serum VEGF and neuropathy could be seen in polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes (POEMS) syndrome, though the patient had no history of a monoclonal gammopathy. The authors suspect this may be elevated in the setting of acute inflammation and repeat testing was pending at time of writing.

To our knowledge, this is the first report of a patient developing CCPD after receiving the first Pfizer SARS-COVID-19 vaccine. In this report, we propose a treatment that has demonstrated a good clinical outcome.

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