TEXAS NEUROLOGICAL SOCIETY

SUMMER 2020

Broca's Area

The Voice of Texas Neurology

President's Message

In previous years, the President's message routinely listed the achievements of the TNS so far and the plans for the year ahead. This year has proven to be the furthest from anything we were accustomed to. It's hard to believe that only 3 months ago we were in Austin attending a great winter meeting with renowned speakers from Texas and all over the nation. It's safe to say that most likely none of us expected all the significant changes that have affected every aspect of our lives since then. Sheltering in place, quarantine, social distancing, personal protective equipment (PPE), telemedicine, are some of the new daily vernacular that has changed our lives since then.

Due to the Covid 19 pandemic, our upcoming summer meeting has been canceled. Based on a brief survey of the members Dr. Eddie Lee Patton, Jr the Co-Chair of the Economic committee produced a special edition of The Business of Neurology video series dedicated to Telemedicine. (You can find a link to the video at the TNS website). Letters to the Governor and our representatives at the US congress and senate to support neurologists with Telemedicine implementation and billing, and ensure PPE availability were cosigned by the TNS together with the TMA and AAN.

Adapting to the changes with the Covid19 pandemic, the TNS will be able to continue to update our members on pertinent legislative and economic issues through its respective committees. Our successful educational grant program will continue with no interruptions. The big question is whether or not we will be able to have our annual meeting next winter. This will be the main point of discussion at our next board meeting in July. We will come up with alternative methods to provide CME activities, display neurology residents' posters, and conduct our business meeting should the winter meeting be canceled due to Covid19.

The tragic death toll of Covid19 and its enormous economic impact will have a lasting effect on all of us for years to come. The challenges this pandemic has brought and continue to impose on us are exhausting, anxiety-provoking, and at times simply scary. Our patients, family, friends, and communities are looking to us for guidance through these uncharted territories. The rational scientific methodology that we all learned and practice as neurologists, and our ability to diagnose and manage challenging diseases prepare us well to take this challenge and help safely guide those who are looking up to us in these difficult times. The TNS will do all it can to support its membership in this journey. I am confident that we will prove to be a more resilient and stronger society when this pandemic is over.

Waleed El-Feky, MD

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Editor's Notes

Randolph W. Evans, MD

THE HISTORY OF HAND WASHING, GLOVES, AND SURGICAL MASKS TO REDUCE IATROGENIC INFECTION IN MEDICINE

In this pandemic, it's interesting to consider the importance of Holmes, Semmelweis, Halsted, and others.

Oliver Wendell Holmes and the transmissibility of puerperal fever. Oliver Wendell Holmes (1809-1894) was a Harvard trained physician who first recognized that puerperal fever was transmissible from physicians to women in 1843., Holmes was one of the most popular authors and poets of his time. His son was the United States Supreme Court Justice.

Semmelweis and hand washing. In this era of hand washing, we remember Ignaz Semmelweis ((1818-1865) who was born in Buda, Hungary and graduated medical school from the University of Vienna in 1844. ,,, In 1846, he was an assistant in the obstetric wards of the Vienna General Clinic where pregnant woman were admitted to one of two wards on alternate days. He was puzzled to discover that the First Clinic had a maternal mortality as much as 4 times greater than the Second Clinic. The only difference he could find was that the First was used to train medical students while the Second trained midwives.

In 1847, the forensic professor at the hospital died from septicemia due to a finger prick by a medical student during an autopsy on a woman who had died from puerperal fever. Semmelweis recognized that the professor had the same sepsis as the woman and concluded that medical students and physicians were carrying "cadaverous particles" from the autopsy rooms to the patients that examined in the First Clinic. Midwives were not involved in autopsies.

On May 15, 1847, Semmelweis ordered everyone to scrub their hands with a chlorinated lime solution which he chose after meeting with the housekeeping staff and looking for the strongest product in use at the hospital. The mortality rate quickly dropped as low in the First Clinic as the Second.

Oliver Wendell Holmes

William Halsted in 1889

In 1848, after a woman with cancer of the uterus with a purulent discharge was examined, 11 out of the 12 women examined consecutively in the ward developed puerperal fever. He concluded that the disease could be spread from necrotic discharges from living patients as well as autopsy material. He recommended hand scrubbing between contacts with each patient.

Semmelweis did not publish an article until 1858 and a book in 1861 ("The Etiology, Concept, and Prophylaxis of Childbed Fever"]. Semmelweis' doctrine was highly criticized because it was contrary to the theory of the time that infections were due to "bad air" or an imbalance of the humors within the body. Hand washing finally made sense with Pasteur's germ theory in 1881 and Koch's postulates in 1882.

When his book was denounced or ridiculed, Semmelweis declared prominent obstetrician as murderers. He became depressed and started drinking. He was taken to an insane asylum in 1865 where he was severely beaten when he tried to escape and died from his injuries.

In death, Semmelweis has been widely memorialized with the eponymous university in Budapest, a postage stamp, a google doodle in March, 2020 during the pandemic, and the subject of movies and plays.

Semmelweis reflex. Semmelweis reflex is characterized by a reflex-like rejection of new knowledge because it contradicts entrenched norms, beliefs, or paradigms.

William Halsted and rubber gloves. Wearing rubber gloves to prevent the spread of infection seems so obvious like handwashing. In 1889, at Johns Hopkins, William Halsted's scrub nurse (and future wife), Caroline Hampton, developed severe contact dermatitis from the cleaning solution. Halsted had Goodyear Rubber Company make her rubber gloves. When his associate, Joseph Bloodgood, reported a dramatically decreased rate of infection after 450 hernia operations wearing rubber gloves, Halsted said, "Why was I so blind not to have perceived the necessity for wearing them all the time?" In the United States, surgical gloves were generally accepted by 1911 and almost universally worn by 1937.

Halsted was one of the great pioneers of surgical history and established the first surgery residency (with many notable residents including Harvey Cushing and Walter Dandy).

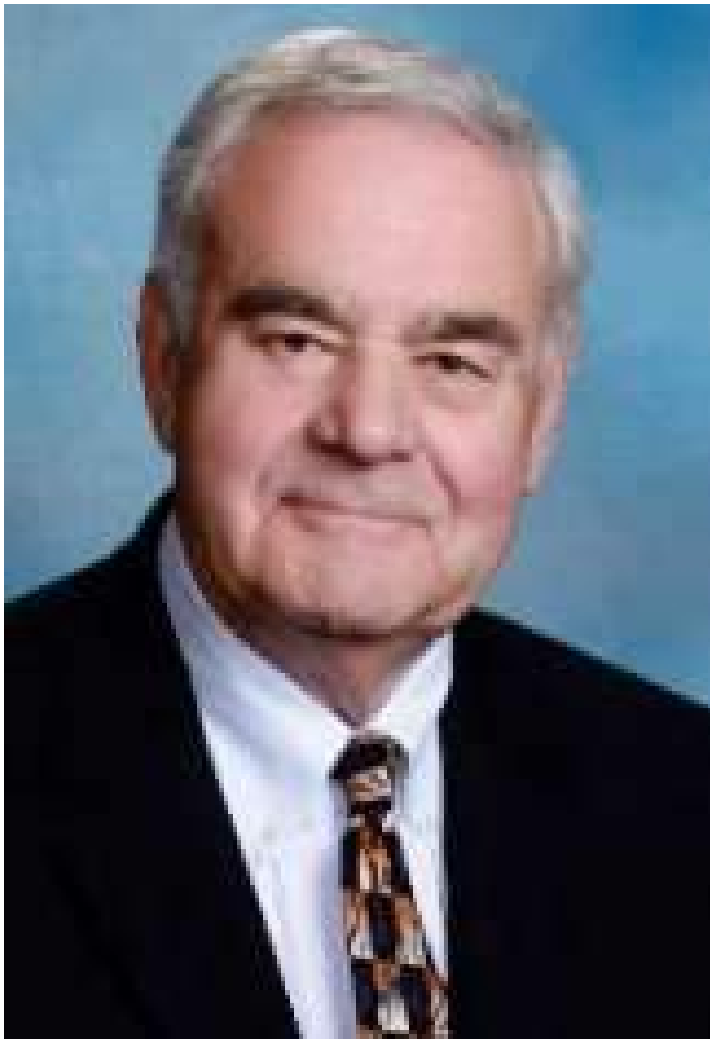
Surgical face masks. In 1897, Fluegge showed that conversation could spread bacterial containing droplets from the nose and mouth substantiating the need for an effective face mask. In 1898, Hueber recommended the use of masks with 2 layers of gauze. In the United States, surgical masks were generally accepted by 1919 and were consistently worn by 1937.[9]

References:

1. Dunn PM. Oliver Wendell Holmes (1809-1894) and his essay on puerperal fever. Arch Dis Child Fetal Neonatal Ed. 2007;92(4):F325–F327
2. Lane HJ, Blum N, Fee E. Oliver Wendell Holmes (1809-1894) and Ignaz Philipp Semmelweis (1818-1865): preventing the transmission of puerperal fever. Am J Public Health. 2010;100(6):1008–1009
3. Pittet D, Allegranzi B. Preventing sepsis in healthcare - 200 years after the birth of Ignaz Semmelweis. Euro Surveill. 2018;23(18)
4. Carson EA, Toodayan N. Ignaz Philipp Semmelweis (1818-1865): herald of hygienic medicine. Med J Aust. 2018 Dec 10;209(11):480-482
5. Kadar N. Rediscovering Ignaz Philipp Semmelweis (1818-1865). Am J Obstet
6. Gynecol. 2019 Jan;220(1):26-39
7. Schreiner S. Ignaz Semmelweis: a victim of harassment? Wien Med Wochenschr.2020 Mar 4
8. Gupta VK, Saini C, Oberoi M, Kalra G, Nasir MI. Semmelweis Reflex: An Age-Old Prejudice. World Neurosurg. 2020 Apr;136:e119-e125
9. Lathan SR. Caroline Hampton Halsted: the first to use rubber gloves in the operating room. Proc (Bayl Univ Med Cent). 2010;23(4):389–392.
10. Adams LW, Aschenbrenner CA, Houle TT, Roy RC. Uncovering the History of Operating Room Attire through Photographs. Anesthesiology. 2016 Jan;124(1):19-24
11. Osborne MP. William Stewart Halsted: his life and contributions to surgery. Lancet Oncol. 2007 Mar;8(3):256-65 Spooner JL. History of surgical face masks. AORN J. 1967 Jan;5(1):76-80

TNS 2020 Lifetime Achievement Award Winner

J. Douglas Hudson, MD



J. Douglas Hudson came to Austin in 1967 following is neurology residency at the University of Iowa. Being only the second neurologist in Austin, Dr. Hudson dedicated himself to growing and improving the community's neurological services. He began this by staffing the Brackenridge Hospital Outpatient Neurological Clinic. In 1970, joined by Dr. Peter Werner, Dr. Hudson founded the Austin Neurological Clinic and opened Austin's first EEG lab with 24-hour monitoring services. With local hospitals reluctant to purchase CT scanners in 1975, Dr. Hudson decided to take matters into his own hands. He, along with some of his colleagues, purchased Austin's first CT brain scanner and eliminated the need to transfer patients to San Antonio or Temple for imaging. They, also, went on to form, Austin Neuro Diagnostics; the first neurochemistry lab and one of Austin's first neurovascular ultrasound labs. Later, the group purchased Austin's first MRI scanner.

To support Austin's growing need for specialized neurological services, Dr. Hudson recruited several neurologists and Austin's first physiatrist, pediatric neurologist and neuropsychologist—all joining Austin Neurological Clinic. He, also, recruited Austin's first neuroradiologist and co-founded one of the nation's first sleep labs in 1980.

Reputed, locally, as the "father of neurology" or the "senior neurologist in Austin", Dr. Hudson played an integral part in the formation of the Austin Neurological Society in 1972. He served as president of the Capital Area Heart Association, board member to several charitable organizations including the local MS Society, Caritas, United Fund and Seton Hospital League House. He, also, served as a neurological consultant to the University of Texas football team and the Women's Athletic Program. While an investigator for L-DOPA trials, shortly before it was approved by the FDA in 1970, Dr. Hudson acquired a sizeable number of Parkinson's patients and went on to establish the Capital Area Parkinson's Society; a society still active today.

In 1975, Dr. Hudson became a charter member of the Texas Neurological Society and joined the board in 1997. He was asked to organize TNS' first winter conference and spent many hours convincing pharmaceutical companies to support the meeting and urging speakers to present. Because of his efforts, the winter conference continues today. Dr. Hudson served as president of the society in 2000.

In recent years, Dr. Hudson has focused his attention on sleep medicine. His passion to explore sleep and its effect on serious health conditions led him to become the first board certified sleep medicine doctor in central Texas and founder of Sleep Medicine Consultants in 2001. In addition to his private practice, hospital and community work, Dr. Hudson is an international speaker, a principal investigator in sleep and neurology-related drug research and a well-respected practitioner in neurology. Dr. Hudson continues to treat patients and educate health care professionals and the public on sleep and other neurological disorders.

TNS Legislative Update: Practicing in the Time of COVID-19

Tom Holloway, TNS Lobbyist & Sara Austin, MD, Legislative Affairs Chair

The term "unprecedented" probably gets thrown around too casually, but it would be understating the matter to describe the COVID-19 pandemic as anything less than a completely unprecedented global health crisis. In a few short months, we've watched this virus exact a devastating toll across the globe, with nearly 300,000 confirmed dead and over 4 million documented infections as of this writing.

Setting aside the extraordinary human costs associated with the coronavirus, this outbreak has also forced a global economic crisis unlike anything we've ever experienced. With millions of Americans sheltering in place, unemployment has skyrocketed to record highs and our once strong national economy is on the verge of an economic collapse not seen since the Great Depression. With businesses and national economies around the world forced into some degree of temporary shutdown, this challenging time has left most of us with more questions than answers when it comes to what the future holds.

It is against this grim backdrop that many Texas neurologists are working to find a way forward and resume something resembling a normal medical practice during a highly abnormal time. Many of you have questions and concerns regarding how to safely conduct in-person patient encounters during this time, and what precautions you should be taking to protect yourselves, your employees, your practices, and of course, your patients.

During this difficult time, the Texas Neurological Society's legislative affairs team has been working to answer these questions and provide some basic information you need to know in order to protect yourself and your practice in the time of COVID-19.

CAN I FACE CRIMINAL LIABILITY FOR PRACTICING DURING THE COVID-19 CRISIS?

On March 13, Governor Greg Abbott declared a state of emergency in Texas and issued the first of several executive orders relating to the coronavirus outbreak. Several days later, Abbott also took the extraordinary step of temporarily suspending all "non-emergency" surgeries and medical procedures to preserve the state's limited hospital capacity, prioritize the deployment of personal protective equipment (PPE), and prevent the Texas healthcare system from becoming overwhelmed with patients.

Since an executive order from the Governor carries the full force and effect of law, any provider practicing in violation of this order would be subject to potential criminal charges, including a fine of up to $1,000 and not more than 180 days in jail.

Fortunately, in the weeks following this declaration, Abbott's COVID-19 Task Force slowly grew more confident that the widespread adoption of social distancing measures and other mitigation strategies had at least modestly "flattened the curve" and forestalled a widespread collapse of the state's critical care system. Facing mounting pressure from frustrated patients and the state medical community, Abbott revised his order on April 17 to allow certain non-emergency medical procedures to resume, provided that they do not impact hospital capacity or deplete the limited supply of personal protective equipment needed to respond to the COVID-19 outbreak.

Though the specific implementation of this order has varied considerably from facility to facility, the governor's revised order has been broadly understood to allow most outpatient and other non-invasive medical procedures to safely resume. Those with questions regarding the conduct of a specific procedure should consult with your admitting facility to ensure appropriate compliance with the governor's order.

CAN I FACE ANY CIVIL LIABILITY FOR PRACTICING DURING THE COVID-19 CRISIS?

On March 27, Congress passed the Coronavirus Aid, Relief, and Economic Security Act ("CARES Act"), a relief and stimulus package that provides federal protection liability protection for all volunteer healthcare professionals that provide medical services during the COVID-19 outbreak.

Section 3215 of the CARES Act states that "a health care professional shall not be liable under Federal or State law for any harm caused by an act or omission of the professional in the provision of health care services during the public health emergency with respect to COVID–19", with exceptions for services provided under the influence, or willful or criminal misconduct, gross negligence, reckless misconduct, or a conscious flagrant indifference.

Of some concern, however, is the fact that the CARES Act only extends liability protection to "volunteer healthcare professionals" — excluding paid physicians who may not be actively treating COVID-19 patients but who nonetheless remain concerned about potential liability associated with treating patients during a novel public health emergency.

Last month, the Texas Neurological Society joined advocates from the larger medical community in lobbying Governor Abbott for additional liability protections for physicians and other healthcare professionals until the emergency declaration is formally lifted. In a letter sent to the governor on April 3, the Texas Medical Association, the Texas Hospital Association, and others formally requested that Abbott use his executive authority to grant expanded liability protection for all Texas healthcare professionals and abate any medical liability litigation resulting from COVID-19 until at least September 1.

Although the governor has yet to take action on this request, we continue to press the issue and will provide an update to the membership as the situation develops further. Perhaps coin-

cidentally, Senate Majority Leader Mitch McConnell recently signaled his intention to push for broad federal liability protections as the centerpiece of any future stimulus and relief package coming out of Washington, DC.

WHAT GUIDELINES SHOULD I FOLLOW IN RESUMING MY PRACTICE SCHEDULE?

For neurologists preparing to resume a standard practice schedule, a number of concerns remain about what precautions are appropriate to help mitigate the potential spread of COVID-19 during in-person patient encounters. On April 30, the Texas Medical Board issued the following regulatory guidance to help keep patients and practitioners safe:

- Posted Notice — all physicians providing patient care or engaging in an in-person patient encounter are required to post a COVID-19 Minimum Standards of Safe Practice Notice in each public area and treatment room or area of the office, practice, or facility.
- Protective Equipment — a mask must be worn by both the patient and physician or the physician's delegate when in close proximity (less than a 6-foot distance), unless removing the mask is necessary to conduct the examination. For any treatment involving a medical procedure or surgery on the mucous membranes (including the respiratory tract) the minimum safety equipment used by a physician or physician's delegate should include N95 masks, or an equivalent protection from aerosolized particles, and face shields.
- Patient Screening — prior to any encounter, patients must be screened for potential symptoms of COVID-19 or verify that they have been screened within last 20 days. It's important to understand that this screening does not require the administration of a coronavirus test and can be conducted verbally to ascertain any patient symptomology that could indicate potential COVID-19 infection.

While following these guidelines will not protect against all civil or regulatory liability arising from the COVID-19 crisis, documenting your practice's strict adherence to these standards can serve as a strong affirmative defense in a civil proceeding or before the Texas Medical Board.

MOVING FORWARD

As physicians and other healthcare providers continue to battle the COVID-19 outbreak, the TNS legislative affairs team will continue to advocate for the best interests of our neurologist members and press for additional relief for medical practices and practitioners that have been impacted by this virus. If you have concerns or suggestions for possible legislative work, please contact our Legislative Affairs Chair, Dr. Sara Austin or our lead TNS Lobbyist, Tom Holloway. Until next time – stay safe, stay healthy, and stay Texas strong!

Telemedicine Has Proven Its Value Past Current Crisis

C. Jones, MD, FAAN, AAN Board Member

In this time of the COVID-19 pandemic, many things have been put on hold, but dramatic and rapid changes have taken place in the way we practice neurology and maintain distancing to protect ourselves, our staff, and our patients. Most notable is the rapid implementation of telemedicine services and the AAN has been at the forefront of helping with this process. However, what happens when the crisis is over? Do we go back to health care as usual? At the AAN, we don't think this is the right future and are actively working to assure that appropriate telemedicine services can continue. My current work as a teleneurologist with a large, national telemedicine company has given me great experience with the process even prior to the pandemic. Before this job, I ran my own solo, private practice in Rhode Island and so I understand the needs and struggles of a business. I currently chair the AAN's Coding and Payment Policy Subcommittee and sit on the Board. These roles have given me novel insight into many aspects of the current environment.

Even prior to the pandemic, the AAN was working on a telemedicine policy to define the uses, legislative and regulatory issues, licensure and liability issues, and coding and payment issues. From webinars to NeuroBytes to FAQs all about the implementation, examination techniques, and pros and cons of telemedicine, AAN members have access to all the resources they need on our website.

But now as this wave of the pandemic seems to be slowing in some areas and everyone is starting to think about opening up safely, the AAN is already hard at work talking to legislators, regulators, and payers to allow the continued use of telemedicine. We strongly feel that our patient population lends itself to the use of ongoing remote monitoring and care. For elderly, low mobility, or chronically ill patients, the use of remote care can lead to better access to care. We understand some patients can't travel well or for long distances, and that disabled or low income patients can't afford the time away from work, and others just need to be monitored more closely at times but not necessarily by coming into the office. The use of telemedicine in concert with interspersed face-to-face visits could improve care for these patients and therefore needs to be available and appropriately compensated for even after the pandemic has ended. We continue to interact with regulators at CMS and provide comments on proposed policies for this year and 2021. We are in discussions with private payers (BCBS, UHC, and Cigna) to work with them on similar coverage policies.

I encourage you to check out the AAN website for current and ongoing resources. We also would like to hear from you with any challenges as well as your experiences with using remote care in your practice (practice@aan.com). Many neurologists already had experience with telemedicine in the setting of stroke care and we have been able to lead the way in appropriately using this technology in other settings.

These are challenging times but the AAN is hard at work to support members and their patients so we can all continue to provide the best care and maintain successful businesses into the future.

The View Into a Virtual Clinic During a Pandemic

Charles T. Gay, MD

About two years ago, a few physicians at Texas Children's Hospital, my section chief included, began piloting telemedicine appointments. It thus seemed likely that we might eventually make video visits a routine part of our practice. In late March, the "we might" changed overnight to "we will." The Texas Medical Board and the Governor had just relaxed regulations for establishing patient-physician relationships by telephone and video, thus paving the way for a rapid transition to virtual visits across the State.

With the need for social distancing in the fourth largest city in the United States, we decided on a Friday to begin transitioning to telephone appointments in child neurology, and by Monday, we had converted most of our appointments to telemedicine. I was amazed at how quickly my friends and colleagues in the clinic mobilized to make it possible for all of us to continue treating our patients, established and new, without interruption.

Our Child Neurology Fellows' Clinic has experienced a similar and relatively seamless transition to virtual visits. Our institution has made the safety of our trainees a priority, so fellows participate in clinic from home right now. After they have "seen" their patients, the fellows locate an available faculty member in a virtual conference room, then peel off to have one-on-one "check-out" conversations about individual patients.

Patients and their families have been similarly quick to adapt to this new style of clinic appointment. Many are thankful that we remain available, while they realize that we are also able to provide in-clinic appointments (using screening and appropriate precautions) when a problem is particularly difficult to assess by telephone or video.

While this transition was rapid out of necessity, and while I would categorize our efforts as successful, no change of this magnitude occurs without glitches and amusing anecdotes.

Some of us work from home, and others at the hospital. I hold virtual clinic in my office because I find it easier to access the electronic medical record, and I also have a chance to interact with our nurses and clinic staff. One downside to a virtual clinic is that I do not have to get up and move around between patients. I must say that my rear end is a bit sore, and my back a little stiffer these days, and I must remind myself to stand, stretch, and take a few steps between patient visits.

I have found telemedicine to be a surprisingly positive and fresh addition. However, in a place that is normally bustling with activity, the halls of the clinic building are quiet. Because of this dramatic shift from in-person encounters, our hospital has made the difficult decision to reduce work hours for the majority of people in the clinics, operating rooms, radiology suites, neurophysiology labs, and therapy centers. Despite this adversity, I am witnessing an amazing spirit and determination among those affected the most: these same people—my friends and colleagues—are somehow finding a way to ensure that we continue providing the best possible care to our patients and their families.

While I know that we will get through this, and while I am confident that we will be stronger on the other side, this certainty does not compensate for the losses that my friends, neighbors, colleagues, and family across the nation are experiencing right now. I just hope that the "other side" of this pandemic arrives soon. Nevertheless, for all of us, I know that soon is still not soon enough.

2020 Annual Winter Conference Poster Winners

First Place: Elsa Rodarte, MD
The University of Texas Health Science Center at Houston
A Tale of Two Arginines: A Case of Compound Missense SPTBN2 and SYNE1 Spectrinopathies

Second Place: Doyle Yuan, MD
UT Houston, Clinical Neurophysiology
Hotspots and Foot Drops: A POEM Case Series

Third Place: Jennifer Murillo, MD
Baylor Scott and White
Types of Brain Tumors in the Central Texas Military and Civilian Populations

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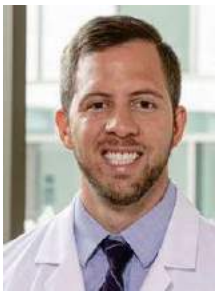
2020 TNS Summer Conference Canceled

After much consideration, TNS Leadership decided to cancel the 2020 Summer Meeting. The TNS leadership continues to monitor the recommendations from the Centers for Disease Control (CDC) and the World Health Organization (WHO), along with numerous travel restrictions issued by companies and medical institutions.

We look forward to seeing you at the 2021 TNS Winter Conference, Feb. 5-7 in Austin!



Erik Krause, DO

Guillain-Barre Syndrome Following SARS-CoV-2 Infection: A Case Report

Erik Krause, DO; Sara Austin, MD; Jessica Erfan, PA-C; Lotika Misra, MD

Dell Medical School at The University of Texas in Austin, Department of Neurology, Austin, TX

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a novel coronavirus which has rapidly spread across the world resulting in a 2019-2020 pandemic. Classically, the virus is associated with fever, myalgia, shortness of breath, and/or respiratory tract illness [2]. However, the spectrum of presentation can vary from mild illness, severe pneumonia, multiorgan failure, and death. Although the primary focus of the virus has centered on respiratory complications, there has been increased awareness for potential neurological involvement [4,6]. As with other viral infections, it is possible that infection with the SARS-CoV-2 virus could be neuroinvasive or could cause a post infectious inflammatory response such as Guillain Barre Syndrome [3]. GBS is an acute or subacute polyradiculopathy which usually presents after a preceding infection which can be either bacterial or viral. Postinfectious GBS has been linked with campylobacter jejuni, cytomegalovirus, influenza A, enterovirus, and many other infectious diseases [7]. GBS has also been associated with the recent Zika virus epidemic [1,5]. The first presumptive case of GBS following an infected SARS-CoV-2 patient was recently reported in China [8]. Our case seeks to bring attention to this potential association and to provide an additional SARS-CoV-2 positive case with associated GBS.

CASE

The patient is a 68 year old male with a history of hypertension, type 2 diabetes mellitus with diabetic neuropathy, and chronic lumbar spondylosis who developed fever, cough and myalgias during a visit to Mexico in the middle of March 2020. His nasopharyngeal swab done on 3/27/20 was positive for SARS-CoV-2. On April 2, 2020 he developed proximal lower extremity weakness along with tingling of both feet and fingertips. The patient recalls difficulty getting out of his car, ambulating up the stairs and required support when walking around his house. He had some mild baseline neuropathy in his feet, but experienced acute worsening of this sensation as well as new paresthesias in his hands. He has a chronic history of lumbar stenosis with low back pain but has been pain-free over the past 2 years. He denied any acute pain, autonomic symptoms, or any bowel/bladder changes. He presented to the emergency room the following day and his vital signs included a temperature of 97.7 degrees Fahrenheit, pulse of 109 beats per minute, blood pressure of 147/95, and oxygen saturation of 98%. On examination, his pupils were normal without evidence of ptosis or ophthalmoplegia. There was symmetrical proximal lower extremity weakness (Medical research council (MRC) grade 4/5 of hip flexors, 4/5 knee flexors).

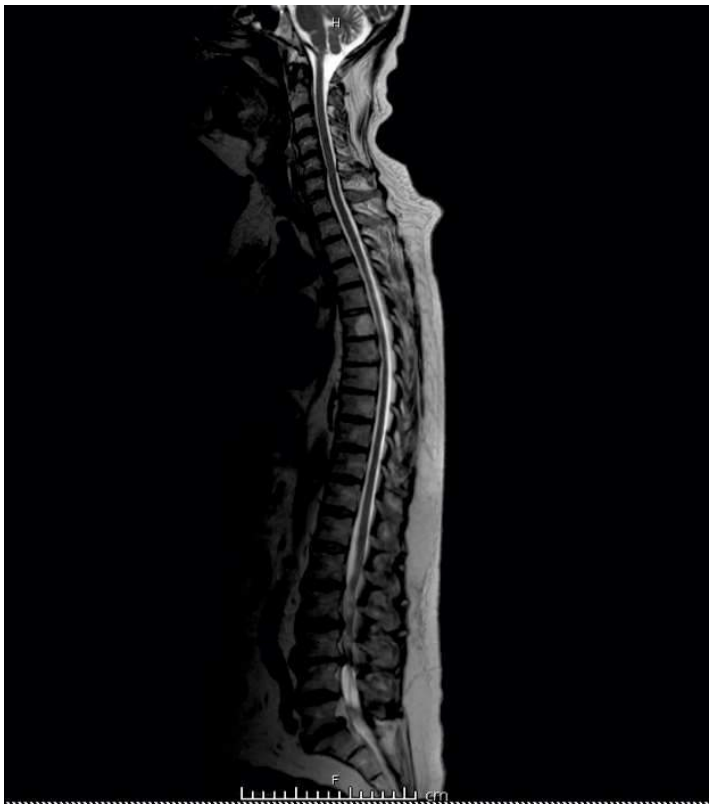


Figure 1: Sagittal T2 MRI of the spine

Vibration and light touch were decreased in both feet and he was areflexic in all four extremities.

Abnormal labs included hemoglobin A1C 7.5 with blood sugars ranging from 133-260, LDH 294 (elevated, normal being 125-224), ferritin 768 (elevated normal 24-336), D-Dimer 599 (normal less than 230), albumin 2.8 (normal 3.2-5.5), cRP 1.9 (normal <=0.5). Complete blood count, complete metabolic panel, creatine kinase, immunoglobulin A levels were all unremarkable. GQ1B IgG antibody and myasthenia gravis panel were both negative.

MRI brain with and without contrast was normal. MRI of the spine with and without contrast showed severe spinal canal stenosis at L3-4 and L5-S1 with moderate to severe degenerative foraminal stenosis bilaterally (figure 1). Smooth nerve root enhancement of the lumbar nerve roots from L3 caudally was also noted (figures 2 and 3). Lumbar puncture revealed elevated protein of 232 mg/dL (range 15-45 mg/dL), normal cell counts of 7 x 10'6 (normal value is less than or equal to 5 uL), and glucose of 86 (range 40-70 mg/dL) (table 1). Nerve conduction studies were not done in order to limit SARS-CoV-2 exposure to equipment and personnel.

The patient was admitted with suspicion for GBS and started on IVIG 1g/kg x 2 days. The following day, the patient developed worsening lower extremity weakness (MRC grades 3/5 hip flexors, 3/5 ankle dorsiflexion) as well as numbness/tingling that had ascended to his shins and up to his elbows. His intrinsic hand muscles (specifically finger dorsiflexion and finger abduction) had also become weak and were rated MRC grade 4/5. The patient started to regain full hand strength by day 6. However, on day 7, he developed a moderate right lower motor neuron type facial weakness. On day 8, his lower extremity strength improved except for knee flexion. Patient

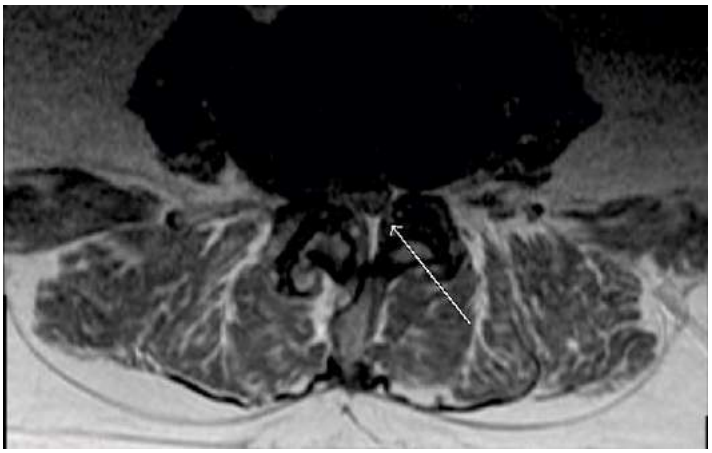


Figure 2: Axial post-contrast T1 MRI with lumbar nerve root enhancement at L4

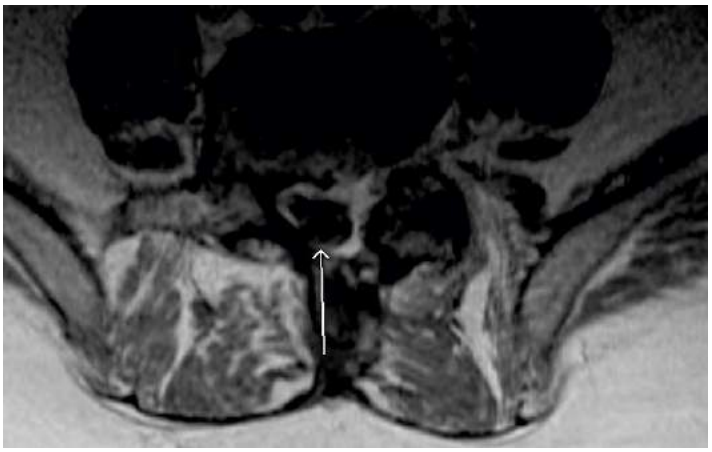


Figure 3: Axial post-contrast T1 MRI with lumbar nerve root enhancement at L5

Clarity CSF	Clear	
Color CSF	Colorless	
RBC CSF	9 uL	Reference Range: (<0)
Glucose CSF	86 mg/dL	Reference Range: 40-70
Protein CSF	232 mg/dL	Reference Range 15-45, Critical High >100
Total Nucleated Cells CSF	7 uL	Reference Range: (<5)
Monocytes CSF	7%	
Neutrophil Granulocytes CSF	6%	
Lymphocytes CSF	87%	

Table 1

had stable respiratory parameters throughout his hospital stay, never requiring supplemental oxygen. Repeat nasopharyngeal SARS-CoV-2 test on 4/10/20 was positive. He was eventually discharged for home intensive physical therapy after a fairly rapid recovery. On discharge, he required a walker to ambulate. He had a repeat ED visit the following day to address severe nocturnal radicular pain in the legs. A repeat contrast MRI of the lumbar spine showed no change and his pain was addressed.

DISCUSSION

SARS-CoV-2 is a deadly pathogen which poses unforeseen daily challenges for the medical community. Aside from the classic respiratory symptoms associated with the virus, reports of neurological involvement have become more apparent. In this case, GBS was identified with classic MRI and CSF changes prompting immediate IVIG treatment. Our patient tolerated the treatment and his clinical course was favorable. His quick clinical response to IVIG is fairly atypical for GBS, however, can be seen in some patients. One limitation is the lack of electrodiagnostic support, but special circumstances regarding SARS-CoV-2 were taken to limit exposure. Since GBS can lead to respiratory failure and even death, it is critically important to identify symptoms and provide early treatment in a respiratory virus such as SARS-CoV-2. This case adds to our expanding knowledge regarding the SARS-CoV-2 pandemic and highlights the need for clinician recognition of potential neurological complications such as GBS.

SOURCES:

1. Brasil P, et al. Guillain-Barre syndrome associated with Zika virus infection. Lancet. 2016; Apr 2; 387 (10026): 1482. PMID 27115821
2. Guan WJ et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020 (published online Feb 28)
3. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. J Med Virol. 2020 Feb 27 (Epub ahead of print). PMID 32104915
4. Mao, L et al. Neurological Manifestations of Hospitalized Patients with COVID-19 in Wuhan, China: a retrospective case series study. JAMA Neurol. 2020 Apr 10. (Epub ahead of print). PMID 32275288
5. Parra B, et al. Guillain-Barre Syndrome Associated with Zika Virus Infection in Colombia. N Engl J Med. 2016 Oct 20; 375: 1513-1523. PMID 27705091
6. Poyiadji N, et al. COVID-19-associated Acute hemorrhagic necrotizing encephalopathy: CT and MRI Features. Radiology. 2020 Mar 31 (Epub ahead of print). PMID 32228363
7. Willison HJ, Jacobs BC, van Doorn PA. Guillain-Barre syndrome. Lancet. 2016 Aug 13; 388 (10045): 717-27. PMID 26948435
8. Zhao H, et al. Guillain-Barre syndrome associated with SARS-CoV-2 infection: causality or coincidence? The Lancet Neurology. 2020 April 1. (Epub ahead of print). PMID 32246917

Impact of COVID 19 on the Field of Neuromuscular Medicine

Aziz Shaibani, MD, Husam AL Sultani, MD
Nerve and Muscle Center of Texas
Houston, Texas

Pandemics have historically induced or expedited permanent changes in many aspects of life and society including medicine.

While it is too early to discover the full impact of COVID 19 on the Neuromuscular medicine, several areas have already witnessed changes. Here are some projections on the topic.

1. Most academic and none academic neuromuscular practices switched to telemedicine and eliminated non-essential physical visits. For years, physicians have been trying to convince the insurance carriers to accept billing for phone visits. COVID 19 did it. Now, any forum that ensures real time video and audio communication is acceptable. HIPPA compliance is loosened during the pandemic. Seeing new patients virtually, is not recommended but will not be audited by the government. I find it difficult to see a none established patient virtually because:
   A. Tertiary care involves extensive review of medical records and detailed neurological examination that are hard to accomplish virtually.
   B. It is hard to provide a diagnosis as drastic as ALS virtually even if the symptoms are clear such as progressive dysarthria and fasciculations of the tongue. Physical visits and body language including eye contact, hand touching and shoulder tapping are still important in clinical medicine especially when it comes to grave diagnoses.
2. More treatable disease like myasthenia gravis also need examination for fatigability and blood testing which is hard to do due to increased risk of exposure . However, if the diagnosis is strongly suspected, Empirical treatment would be acceptable to avoid respiratory involvement which would increase mortality with COVID 19. .
3. Initiation of steroids and steroid sparing agent during COVID 19 is not recommended especially in the elderly. IVIG has the advantage of enhancing (or at least not depressing) immunity as opposed to other modalities. Eculizumab and other complement inhibitors are not recommended because they may increase the risk of viral infection.
4. Blood monitoring during administration of steroid sparing agents will need to be individualized due to the increased risk of exposure during testing.
5. Patients with stable or progressive but chronic neuropathies can wait until the end of the pandemic.
6. Symptomatic treatment may be considered for patients with myalgia, muscle cramps or neuropathic pain until full evaluation becomes possible.
7. Patients with neuromuscular disorders are at a higher risk for COVID 19 infection and complications, therefore extra efforts are to be taken for social distancing (facial masking, frequent hands washing, etc).
8. Neuromuscular respiratory compromise is hypercapnic while COVID 19 interstitial pneumonitis is hypoxic. Optimal ventilatory settings would be challenging.
9. The most commonly reported COVID 19 treatment candidates are hydroxychloroquine and azithromycin, both will have to be used cautiously in MG.
10. Participants of neuromuscular trials may increase their risk of exposure by traveling to the research sites. Most sponsors and IRBs are allowing remote visits. Impact of the experimental agents on COVID 19 risk is to be studied carefully.
11. 5 cases of GBS in associated with COVID 19 were reported (NEJM, April 17, 2020). No distinguishing features were noted except that none had evidence of dysautonomia. No polio like syndrome similar to the one caused by WNV infection is reported. The virus does not seem to have a neurotropic property . Headache and seizures are suspicious of encephalopathy. It is not clear if this is due to direct viral invasion or due to respiratory failure. So far viral encephalitis is not documented pathologically. PCR did not recover COVID 19 DNA in the CSF of the affected patients.
12. Myalgia and mild CK elevation are not specific and are common in viral infections.
13. Elevated CK is associated with high mortality, maybe due to dissemination of infection.
14. Neuromuscular tele-examination can be done but DTRs, pupillary reflexes and fundoscopic examinations are hard to obtain. Gait, speech, mental status, strength, sensation , coordination, facial strength, tongue exam, hearing, and vision can be assessed.
15. Testing requires physical presence:
   A. EMG/NCS and muscle/nerve/skin biopsies obviously needs physical presence. The same applies to MRIS , autonomic testing, LP, and blood testing.
   B. One can do a preliminary evaluation remotely and schedule the procedures once the pandemic is gone if the clinical status allows. However, once a relationship is established, the physician will be responsible for answering calls about symptoms, providing refills, etc.
   May be in the future, patients who live far away, be assessed initially virtually and appropriate labs are ordered to be discussed during the physical visit. That way, patients can be saved visits.
16. The heroes of the pandemic have been the health care professionals and NM doctors are among them. Many of them are in the front lines. They have to take calls and sometimes visit ERs. Already several NM doctors got sick and some died. The world and profession are indebted to their services.
17. Telemedicine is not without deficiencies. It is not easy to use in elderly, many of them do not know how to use Zoom or skype and do not have iphones. However, once they see the benefit of remote visits, they will be motivated to learn. Hearing impairment is as challenging. Recording of the encounter without permission and posting partial segments in the social media will be an issue. Regulations to deal with this aspect will be emerging.

Ponto-Meso-Diencephalic Involvement in Neuro-Behçet's Disease

Shin C. Beh, MD
Department of Neurology, University of Texas Southwestern Medical Center

CASE STUDY

A 34-year-old previously healthy Italian woman was admitted with a 3-day history of fever, progressive lethargy, holocephalic throbbing headaches, and intermittent binocular vertical diplopia. There was no history of recent travel, illness or immunization.

On examination, she was drowsy but arousable and could follow commands. Her pupils were equal and reactive to light and accommodation. Ophthalmoscopy was normal. Visual field examination revealed a right homonymous superior quadrantonopsia. Ocular ductions and versions were normal, and no nystagmus was observed. The remainder of the neurologic examination was remarkable for dysarthria, left upper limb dysmetria, and gait ataxia. No dermatologic lesions were observed.

Laboratory studies (serum B12, thyroid panel, paraneoplastic panel, erythrocyte-sedimentation rate, angiotensin-converting enzyme, lupus-anticoagulant, anti-GQ1b antibodies, rapid plasma reagin, and serologic studies for Bartonella, Brucella, Mycoplasma pneumoniae, Listeria monocytogenes, and human immunodeficiency virus) were unrevealing. Cerebrospinal fluid (CSF) analysis was remarkable for 260 white blood cells/mm3 (94% lymphocytes) and elevated protein (56 mg/dL). CSF viral PCR (JC virus, Epstein-Barr, parvovirus-B19, herpes-simplex, varicella-zoster, and human herpesvirus-6), gram stain, acid-fast stain, West-Nile virus IgM, culture, IgG index, IgG synthesis rate, oligoclonal-bands, and cryptococcal antigen were unremarkable.

Brain MRI revealed a fluid attenuation inversion recovery (FLAIR) hyperintense lesion with subtle enhancement in the midbrain and pons, extending into the upper medulla, left diencephalic region, left medial temporal lobe, and left hippocampus (Figure 1). Magnetic resonance angiography and venography were unremarkable.

A more detailed interview with the patient's family revealed a history of recurrent oral and painful vaginal ulcers. A diagnosis of neuro-Behçet's disease (NBD) was made. Intravenous methylprednisolone 1g daily and immunoglobulin (IVIG) 400 mg/kg/day were administered for a total of 5 days. By the third day, she was fully alert with some minor trouble with recalling the events of the past week. Upon completing methylprednisolone and IVIG therapy, she had returned to her baseline and the only symptom remaining was intermittent binocular vertical diplopia.

DISCUSSION

Behçet's disease is an idiopathic, chronic, relapsing, multisystem vascular inflammatory disease characterized by recurrent mucocutaneous ulcers.1 The intermittent oral ulcers that characterize Behçet's disease are painful, erosive lesions with white yellowish necrotic bases surrounded by red areolae. The genital ulcers may be painless and usually affect the scrotum and inguinal regions in males, and the vulva and femoral-inguinal areas in females.1,2 The disease is more common in countries along the ancient Silk Route, but is rare in Europe and North America.1-3 NBD affects between 3-9% of patients with Behçet's disease, with a male predominance.3 Table 1 summarizes the systemic manifestations of Behçet's disease.1-3

NBD can be divided into non-parenchymal, and parenchymal disease; patients with non-parenchymal disease rarely have concomitant parenchymal involvement.1,2 Parenchymal disease is more common, and brainstem lesions occur in half.2 Non-parenchymal disease is characterized by cerebral venous sinus thrombosis, typically affecting the superior sagittal and transverse sinuses.1,2 Venous sinus thromboses can result in intracranial hypertension.1-3 Infrequently, arterial disease, or an acute meningeal syndrome may occur in non-parenchymal NBS.1,3 Table 2 summarizes the manifestations of NBD.

On MRI, NBD lesions are large, poorly-demarcated, T1-isointense, T2/FLAIR-hypertense, with variable contrast enhancement, and most commonly located in the mesodiencephalic region, followed by the pontobulbar area.1,5,6 The extension of the lesion from the thalamus to the midbrain is sometimes referred to as the cascade sign.2 Acutely, secondary extension towards the basal ganglia and/or medulla due to vasogenic edema may also be seen.1,6 Rarely, NBD lesions appear mass-like, mimicking the appearance of tumors or lymphoma.5,6 With time, atrophy of these affected areas, with corresponding T1-hypointense signal, may be observed.1,5,6

Acute attacks or relapses should be treated with high-dose corticosteroids, typically intravenous methylprednisolone 1000 mg/day for 5-7 days, followed by an oral taper over 2-3 months.2 Those with relapsing or progressive disease should be treated with immunosuppressive therapies like mycophenolate, methotrexate, or cyclophosphamide.2

In conclusion, NBD should be suspected in patients with mesodiencephalic lesions on neuroimaging. The relevant history should be elicited should be undertaken to confirm the diagnosis.

REFERENCES

Kalra S, Silman A, Akman-Demir G, et al. Diagnosis and management of Neuro-Behçet's disease: international consensus and recommendations. J Neurol 2014;261:1662-1676

Borhani-Haghighi A, Kardeh B, Banerjee S, et al. Neuro-Behcet's disease: an update on diagnosis, differential diagnoses, and treatment. Mult Scler Relat Disord 2019;39:101906

Kidd DP. Neurological complications of Behçet's syndrome. J Neurol 2017;264:2178-2183

Al-Araji A, Kidd BP. Neuro-Behçet's disease: epidemiology, clinical characteristics, and management. Lancet Neurol 2009;8:192-204

Uygunoglu U, Siva A. Behçet's syndrome and nervous system involvement. Curr Neurol Neurosci Rep 2018;18:35

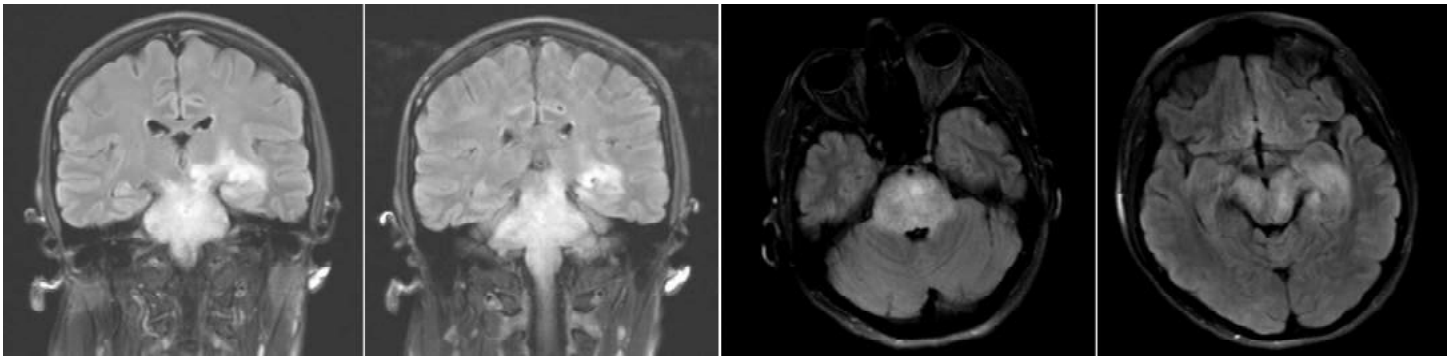
Mehdipoor G, Davatchi F, Ghoreishian H, Arjmand Shabestari A. Imaging manifestaitons of Behçet's disease: key considerations and major features. Eur J Radiol 2018;98:214-225

SYSTEM	MANIFESTATIONS
Dermatologic	Oral aphthous ulcers, genital ulcers, anorectal ulcers, pseudofolliculitis, erythema nodosum, uperficial thrombophlebitis, papulopustular lesions, and vasculitic ulcers
Ophthalmic	Uveitis, retinal vasculitis
Gastrointestinal	Esophageal ulcers, acute abdomen, proctorrhagia, chronic recurrent diarrhea, gastroduodenitis
Vascular	Deep vein thrombosis, Budd-Chiari syndrome, arterial thromboses, aneurysm
Joints	Arthralgia, arthritis (mono-, oligo-, or poly-arthritis)

Table 1: Systemic manifestations of Behçet's disease

Parenchymal	Hemispheric	Headache, sensorimotor deficits, seizures (focal epilepsy, generalized epilepsy, myoclonus), cognitive impairment, movement disorders (parkinsonism, chorea, tics, dystonia, oculopalatal tremor), acute confusional state, psychiatric disorders (mania, psychosis, kleptomania), sleep disorders (late-onset non-rapid eye movement sleep, sleep apnea, restless leg syndrome)
	Meningeal	Pacyhmeningitis, leptomeningitis, aseptic meningitis
	Brainstem	Ophthalmoplegia, sensorineural hearing loss, Horner syndrome, facial weakness, cerebellar ataxia, pseudobulbar palsy
	Spinal Cord	Longitudinally-extensive transverse myelitis
Non-parenchymal	Venous	Central venous sinus thrombosis (usually affecting the superior sagittal sinus, transverse sinuses, deep cerebral veins, and cavernous sinus), intracranial hypertension
	Arterial	Stenosis, aneurysm, dissection, hemorrhage (intraparenchymal, subarachnoid), ischemic infarcts, vasculitis

Table 2: Summary of NBD manifestations



Brain MRI (coronal view in the first and second panels, and axial view in the third and fourth) reveal a fluid attenuation inversion recovery (FLAIR) hyperintense lesion involving the whole midbrain and pons, extending into the upper medulla, left diencephalic region, left medial temporal lobe, and left hippocampus.

General Anesthesia and Long-Term Neurodevelopmental Implications

Leah Ferrante, MD, Neurodevelopmental Disabilities Fellow, Baylor College of Medicine

Sarah Risen, MD, Assistant Professor Pediatric Neurology and Developmental Medicine Baylor College of Medicine / Texas Children's Hospital

INTRODUCTION

Anesthesia is a state in which there is induced, temporary loss of sensation and/or awareness and is a routine part of patient care to minimize both physical and psychological harm during diagnostic and surgical procedures1. While many short term side effects have been noted such as post-procedure nausea, dizziness and prolonged sedation, there has been particular interest in its long term effects on the central nervous system, especially concerning children whose nervous systems are not yet fully developed. While some early animal studies indicated that there are dose-dependent neuroprotective benefits2, results from recent in vivo and in vitro studies indicate adverse effects of anesthesia on developing neurons. Several clinically relevant studies suggest significant differences in neurodevelopmental outcome in children, including slower processing speed, poorer fine motor skills and increased behavioral issues, years after anesthesia exposure, even when correcting for other potential confounding variables3, 4. Considering an estimated 1 million pediatric procedures requiring anesthetics were performed in the United States in 20155, awareness of developmental anesthetic neurotoxicity is invaluable and relevant for all physicians, particularly neurologists.

Proposed Mechanism of Anesthetic Induced Neuronal Injury

Anesthetics have multiple different mechanisms of action, but each ultimately increases the threshold for neuron depolarization, primarily through GABAa receptors. Different anesthetics have been shown to also act through nicotinic acetylcholine receptors, glutamate receptors, glycine receptors, and voltage gated sodium and potassium channels. The end result of anesthesia is an overall depression of the nervous system.

Far more studies describe the mechanism of neuronal injury resulting from inhalational anesthetics compared to intravenous anesthetics. However, both inhalational and intravenous anesthetics have been shown to result in neuronal apoptosis in vitro through multiple mechanisms including mitochondrial oxidative phosphorylation decoupling and energy failure, protein misfolding, inability to digest cellular by-products and caspase activation directly injuring neurons2. In particular, the dentate gyrus of the hippocampus, striatum and the subventricular zone continue neurogenesis beyond birth, leaving these areas as the most vulnerable to developmental anesthetic neurotoxicity in infants and young children10. In a study by Stratmann et al, rats (7 days postnatal) equivalent to human infant age were exposed to isoflurane, an inhalational anesthetic. Age matched controls and anesthesia exposed groups both were injected with bromodeoxyuridine (BrdU), a nucleoside that is used to identify cell proliferation. On microscopy, the exposed group that received BrdU injections during isoflurane exposure had significantly less BrdU+ neurons in the dentate gyri than the controls6. Anesthetic developmental neurotoxicity results from this type of injury to the central nervous system during critical periods in neurodevelopment.

Neurodevelopmental Sequelae

The human brain has most of its neurons by the time an infant is born at term but there are significant changes that continue to occur in neurons including synaptogenesis, receptor aggregation, developmental switching in receptor subunits, dendritic pruning etc., all of which could potentially be interrupted or altered by anesthesia exposure. Premature infant brains have additional risk as their nervous systems are even more immature and premature infants often undergo procedures requiring anesthesia.

In the prior mentioned study by Stratmann et al6, the young rats exposed to isoflurane and age-matched controls also underwent learned fear response testing, a measure of learning mediated by the hippocampus. While there was no significant difference in performance between the two groups at 15 days and 26 days after anesthesia exposure, 5 months post-exposure showed a significant decline in fraction of time the tones led to fear response, implying there may have been an interruption in normal learning processes in order for the exposed rats to retain their fear response. The authors explain that this finding could correlate to the neuropathologic finding of reduced BrdU+ neurons in the dentate gyri of anesthesia exposed groups.

While animal studies demonstrated concern for developmental anesthetic neurotoxicity since 20038, the first study indicating potential neurodevelopmental consequences in children following anesthesia was in 2009 by DiMaggio et al7. This initial retrospective cohort study reviewed charts of 383 children that underwent hernia repair with anesthesia prior to age 3 and 5050 age matched controls that did not have hernia repair, a guaranteed general anesthesia exposure. The group does specify that it's possible their control group subjects may have had general anesthesia, though it was not guaranteed compared to the other group. Each group was analyzed for the frequency of ICD-9 codes associated with neurodevelopmental disabilities including "unspecified delay or behavioral disorder", "mental retardation", "autism", and "language or speech problems". Significantly more children in the anesthetic-exposed group had co-occurrence of one of the listed ICD-9 codes compared to the unexposed group (4.4% and 1.2 % respectively), with children exposed to anesthesia before 3 years of age being 2.3x more likely to have a neurodevelopmental diagnosis. As many neurodevelopmental disabilities result in lifelong functional impairments, this study emphasized the importance of better understanding the effects of anesthesia on development.

Further exploring the neuropsychological consequences of anesthetic exposure, Stratmann et al3 evaluated specific recognition memory tasks (familiarity and recollection) in 28 children 6-11 years old that had undergone general anesthesia prior to 2 years of age and 28 healthy age-matched children without a history of inhalational anesthesia administration. Familiarity is mediated by the anterior medial temporal lobes and perirhinal cortex, areas where neurogenesis does not persist beyond birth, whereas recollection is mediated by the hippocampus and anterior thalamic nuclei, areas known to have persistent neurogenesis into adulthood. There was no difference between the two groups in their abilities to become familiar with objects, but recollection of specific details presented was significantly impaired in the group of children that had received anesthesia prior to 2 years of age. This study further raises concern that early disruption of neurogenesis in specific neural regions with anesthesia can result in long-term functional deficits.

Further studies have found similar association between anesthesia and long-term neuropsychological impairments. In a study by Warner et al4 , nearly 1000 children including 411 healthy controls and 586 children exposed to general anesthesia (380 with a single exposure and 206 with multiple anesthetic exposures) underwent comprehensive neuropsychiatric evaluation. While there was no significant difference found in overall IQ between the three groups, testing results identified that the children with multiple anesthetic exposures had significantly more impaired processing speech and fine motor skills as well as more significant behavioral and emotional issues. While it remains unclear the specific variables of anesthesia, such as total anesthetic dose or length of exposure time, that results in neurodevelopmental impairments, this study raises notable concern about the potential detrimental effects of multiple anesthetic exposure in young children.

Intravenous anesthetics have also been shown to cause developmental anesthetic neurotoxicity in children. Yan et al9 prospectively followed 49 healthy infants and children undergoing up to 3 outpatient laser surgeries for benign facial growths up to age 22 months. Bayley Scales of Infant Development, (the gold standard assessment of development in young children) were performed and S-100β level (a biomarker associated with central nervous system injury) were obtained prior to each procedure and again 3 days after the final procedure. Every child was sedated with only 1 dose of ketamine per procedure and all procedures lasted less than 5 minutes. Mental and psychomotor indices were lower in all 3 groups compared to pre-anesthesia scoring but only reached statistical significance in the group of children undergoing three procedures. Additionally, S-100β levels were significantly higher after the final procedure in all three groups, raising concerns of central nervous system injury even with a single dose of ketamine. This study suggests possible rapid neurodevelopmental injury and deficits from ketamine exposure in infants and young children; however, it remains unknown if these developmental deficits ultimately result in long-lasting impairments or were only transient findings.

Another interesting area of research focuses on the response to anesthetics based on a specific genotype. Based on the clinical observation that autistic children with Shank mutations tend to recover much slower after anesthetic administration than their neurotypical peers, Li et al11 evaluated the response of Phelan McDermid-like mice with Shank3+/ΔC mutation to general anesthesia. Consistent with clinical experience, the Shank3+/ΔC mice required significantly less anesthesia to achieve appropriate sedative and analgesic effects compared to their wild-type peers. It will be important to obtain a better understanding of genotypic susceptibility to the effects of anesthesia in order to assist with the dose and possibly even type of anesthesia used in effort to minimize neurodevelopmental toxicity.

Conclusion

Anesthesia, while overall beneficial and necessary, may be associated with developmental anesthetic neurotoxicity and long-term neurodevelopmental deficits. Physicians should be aware of emerging clinical data and order studies requiring anesthesia thoughtfully and judiciously. While neurologists are certainly not the only specialty that utilize anesthesia, we may be the medical providers to diagnose and manage the long-term adverse neurodevelopmental effects in the form of cognitive, learning, fine motor, and behavioral issues. Considering this early evidence, alternatives to minimize anesthesia exposure, most prominent of which are child life services, should be utilized when possible. Neurologists can be advocates for our patients by decreasing out use of anesthesia for routine procedures such as an MRI scan or lumbar puncture, or by attempting to combine procedures that require anesthesia whenever possible. The potential risk of anesthetic associated neurotoxicity may not be avoidable in many patients, but we can meaningfully impact a child's long-term neurodevelopment by maintaining an awareness of the concern and staying up to date on the evidence as studies about the neurodevelopmental effects of anesthesia continue to emerge.

References:

1. Son, Y. Molecular Mechanisms of General Anesthesia. Korean Journal of Anesthesiology. 2010; 59: 3-8.
2. Yang M, Wei H. Anesthetic neurotoxicity: Apoptosis and autophagic cell death mediated by calcium dysregulation. Neurotoxicology and Teratology. 2017; 60: 59-62
3. Stratmann G et al. Effect of General Anesthesia in Infancy on Long-Term Recognition Memory in Humans and Rats. Neuropsychopharmacology. 2014; 39:2275-2287.
4. Warner D et al. Neuropsychological and behavioral outcomes after exposure of young children to procedures requiring general anesthesia: The MASK study. Anesthesiology. 2018; 129: 89-105.
5. Muffly M et al. The Pediatric Anesthesiology Workforce: Projecting Supply and Trends 2015-2035. Anesthesia & Analgesia. 2018; 126: 568-578.
6. Stratmann et al. Isoflurane Differentially Affects Neurogenesis and Long-term neurocognitive Function in 60-day-old and 7-day-old Rats. Anesthesiology. 2009; 110:834-848.
7. DiMaggio et al. A Retrospective Cohort Study of the Association of Anesthesia and Hernia Repair Surgery with Behavioral and Developmental Disorders in Young Children. Journal of Neurosurgical Anesthesiology. 2009; 21:286-291.
8. Jevtovic-Todorovic et al. Early Exposure to Common Anesthetic Agents Causes Widespread Neurodegeneration in the Developing Rat Brain and Persistent Learning Deficits. Journal of Neuroscience. 2003; 23:876-882.
9. Yan J, Li Y, Zhang Y, Lu Y, Jiang H. Repeated Exposure to Anesthetic Ketamine Can Negatively Impact Neurodevelopment in Infants: A Prospective Preliminary Clinical Study. Journal of Child Neurology. 2014; 29: 1333-1338.
10. Kang E et al. Neurogenesis and developmental anesthetic neurotoxicity. Neurotoxicology and Teratology. 2017; 60: 33-39.
11. Li C et al. Sensitivity to isoflurane anesthesia increases in autism spectrum disorder Shank3+/Δc mutant mouse model. Neurotoxicology and Teratology. 2017; 60: 60-74.

Contractures in Myopathies

Aziz Shaibani, MD, Husam AL Sultani, MD
Nerve and Muscle Center of Texas
Houston, Texas

QUESTIONS:

Q1/ A 34-year-old man who walked on his toes as a child and had Achilles tendon surgery. As he grew older, he developed weakness of the triceps and knee flexors and extensors. He had two healthy brothers and no family history of muscle disease. Examination findings are shown in the vide number 1. CPK was: 477 IU/L, Electromyography (EMG) showed mixed long and short duration MUAPs in the tested proximal muscles. (see video 1)

Cardiac involvement is typically a feature of the following myopathy:

A. Oculopharyngeal muscular dystrophy (OPMD)
B. Emery-Dreifuss muscular dystrophy (EDMD)
C. Facioscapulohumeral muscular dystrophy (FSHD)
D. Collagen VI myopathies

Q2/ A 32-year-old woman who walked on tiptoes at age 5 years for which she had an elongation of the Achilles tendon bilaterally. She had one healthy sister and no family history of muscle disease. She developed a fixed mild proximal legs weakness since childhood. CPK level was slightly elevated and EMG was myopathic. Physical findings are shown in video 2.

Contractures are common in the following myopathies:

A. Limb Girdle muscular dystrophy type 2 B (LGMD2B)
B. Myotonic dystrophy
C. Bethlem myopathy
D. FSHD

Answers:

Answer 1: B-Blood genetic testing revealed a heterozygous pathogenic mutation in Lamin A (LMNA) gene, confirming EDMD

Answer 2: C- Blood genetic testing revealed a Heterozygous De Novo Pathogenic mutation of Collagen 6 A2 (COL6A2) gene confirming Bethlem myopathy.

DISCUSSION:

It is important to differentiate between metabolic contractures, a feature of some metabolic myopathies which are painful, occur during exercises and are electrophysiologically silent, and myopathic contractures which limit passive stretch ability of a muscle to its proper length due to fibrosis. While most advanced myopathies are associated with contractures due to fibrosis, the development of contractures while the muscles are still functional, is a feature of only a few myopathies.

Contractures are an important diagnostic clue, especially, most of the contractures-associated myopathies carry no other specific features (normal or mild CK elevation, myopathic EMG and muscle biopsy). Such differentiation is important to select the right genetic testing and to facilitate the identification of some fatal myopathies due to cardiac arrhythmias which can be prevented by a defibrillator and or a pacemaker. Toe walking during childhood is an important sign of contracture of the calf muscles and many patients undergo surgical repair of the Achilles tendon for it. Such a finding should prompt a search for other contractures and a family history of muscle disease or sudden death.

There are two major groups of myopathies with contractures:

1. Bethlem myopathy: this is characterized by:
   - It is caused by Collagen VI mutations in one of the three collagen VI genes COL6A1, COL6A2 and COL6A3
   - Mutations cause two main types of muscle disorders: Ullrich congenital muscular dystrophy, an autosomal recessive disease with a severe phenotype, and a mild to moderate phenotype, Bethlem myopathy which is usually autosomal dominant.
   - Clinically, this group is characterized by muscle and connective tissue involvement, including weakness, joint laxity and contractures, and abnormal skin findings. Bethlem myopathy is proximal and contractures are characteristically distal, affecting finger flexors and to a lesser extent, they affecting ankles and elbows.
   - Although considered benign, 10% of patients need nocturnal respiratory support and 2/3 of patients require a walking aid after age 50 years.
   - Cardiac involvement is rare.
2. Emery-Dreifuss muscular dystrophy (EDMD): this is characterized by:
   - Early contractures, often before any significant weakness, of elbows, Achilles tendons, and post-cervical muscles
   - Slowly progressive muscle wasting and weakness with a distinctive humero-peroneal distribution (i.e. proximal in the upper limbs and distal in the lower limbs) early in the course of the disease.
   - Cardiac conduction defects (ranging from sinus bradycardia, prolongation of the PR interval on electrocardiography to complete heart block). Cardiomyopathy may also supervene. Thus, affected individuals may die suddenly from heart block, or develop progressive cardiac failure.
   - Responsible mutations affect Emerin and Lamin A and C genes. There are two main modes of inheritance; X-linked (Emerin) and autosomal dominant (Lamin). Rare autosomal recessive inheritance has also been described. EDMD can be also caused by mutation of FHL1 and SYNE genes.

Teaching points:

1. Toe walking history should prompt a search for contractures of other joints and family history of muscle disease or sudden death.
2. If contractures are out of proportion to weakness, consider EDMD
3. If finger flexors are contracted, consider Bethlem myopathy
4. Cardiac monitoring is essential for all EDMD patients.

Video Links:
https://1drv.ms/v/s!AuM2slBEjNxNhVE0j-dx1tNy1jB6?e=yOVcT8
https://1drv.ms/v/s!AuM2slBEjNxNhVDmnWYGiQGsDJ-P?e=1aZXd5

References: Contractures and muscle disease. R. Jon Walters. Pract Neurol 2016;16:258-263


Erin Furr Stimming, MD

Telemedicine in Movement Disorders

Erin Furr Stimming, MD

Associate Professor, Neurology; Director, Neurology Clerkship; Director, HDSA Center of Excellence, Department of Neurology, The University of Texas Health Science Center at Houston

Jorge Patiño, MD, Research Assistant, Department of Neurology, The University of Texas Health Science Center at Houston


Jorge Patiño, MD

During the last decade multiple efforts have been underway to increase access to healthcare to underserved populations, patients in rural areas and/or those who have chronic health conditions that limit their ability to travel through telemedicine. However, we have been restricted in our ability to effectively implement telemedicine in the outpatient setting largely in part to constraints in reimbursement. Due to the coronavirus pandemic, telemedicine in the outpatient setting has been quickly adopted throughout many neurology clinics around the world. The flexibility and adaptability of our colleagues and patients has been extraordinary. This short review highlights multiple relevant studies that have focused on evaluating various movement disorders virtually.

Telemedicine is divided into two types, synchronous and asynchronous. Synchronous telemedicine is defined as a live interaction between the healthcare provider and the patient, an example of this is video conferencing. Asynchronous telemedicine is defined by the storing of information to be transmitted from the patient over a period and in separate time frames (Srinivasan et al., 2020) such as a smart home or digital body sensors.

Telemedicine programs, while successful in the setting of acute stroke and inpatient neurology, have not previously been widely adopted in the outpatient setting. Despite the lack of widespread acceptance, novel approaches have been suggested to treat and follow patients with movement disorders, such as adapting previously validated rating scales, modifying the collection of data and relying on synchronous and asynchronous data.

One of the well-recognized advantages of telemedicine is the facilitation of care for patients with limited mobility due to a neurodegenerative disease, which makes travel particularly difficult (Hanson, Truesdell, Stebbins, Weathers, & Goetz, 2019; Seritan, Heiry, Iosif, Dodge, & Ostrem, 2019; Srinivasan et al., 2020). Evidence shows that more than 40% of patients with Parkinson's disease (PD) do not receive care from a neurologist, making them prone to being placed in nursing facilities, increasing their risk of hip fracture and increasing the likelihood of death (Ben-Pazi et al., 2018). Therefore, it is imperative we devise new strategies through telemedicine to better care for these patients and in fact multiple telemedicine studies have been done focusing on PD. Five randomized controlled trials have been completed that compared telemedicine to in-person care for individuals with PD and quality of life was found to be improved or similar (Ben-Pazi et al., 2018; Dorsey et al., 2010; Group GBD 2015, 2017). Telemedicine has also been found to be more cost effective as the costs associated with travel time are eliminated (Ben-Pazi et al., 2018; Cubo et al., 2017; Wilkinson et al., 2016). While evaluating patients virtually does limit some assessments, relevant data can still be collected and in fact, a modified version of the Unified Parkinson's Disease Rating Scale (UPDRS), without the ability to test for rigidity and postural instability, has been found to be valid and reliable (Ben-Pazi et al., 2018; Bull et al., 2014; Srinivasan et al., 2020).

In general, like all technologies relying on internet connection, there are concerns that factors such as connectivity, video and image quality could contribute to a negative experience. However, studies have reported that when balancing factors such as travel and expenses, telemedicine is favored by both patients and healthcare professionals (Hanson et al., 2019).

In the context of movement disorders, there are some concerns regarding the accuracy of information that can be retrieved with the help of telemedicine. Many patients have symptoms and signs that could be intermittent, typically home-based or that require longer observation periods (Ben-Pazi et al., 2018). For example, tremor evaluation could be limited by the quality of the video and there needs to be an optimal functioning of the hardware and software. In this case, it is recommended to also implement asynchronous telemedicine to overcome this issue (Srinivasan et al., 2020). Newer technologies like digital sensors for kinematics have been found to be helpful following patients' symptoms (Albani et al., 2019), and novel approaches are being studied to improve the rehabilitation process (Lei et al., 2019). Among other concerns, patients with tremor need a comprehensive physical examination so that its phenotype can be distinguished (i.e. resting, kinetic, postural, intention, orthostatic). However, it has been shown that telemedicine effectively allows for this assessment.

For patients with tics, it has been recognized that they are less pronounced when the patient is examined face-to-face, therefore, telemedicine could be more helpful for addressing these patients (Ben-Pazi et al., 2018). Some studies have suggested that telemedicine could be helpful for the behavior-

al therapy interventions and the need for frequent repeat visits. Tools like TicHelper.com provide an interactive module treatment program (Ben-Pazi et al., 2018). However, it has not been deeply evaluated and additional studies should be done to assess patients' adherence and clinical improvement (Srinivasan et al., 2020).

For patients with dystonia, synchronous and asynchronous telemedicine can be very helpful, but need a good quality and resolution so that any detail will not be missed. Also, patients can benefit from an integral approach including psychological interventions. One of the limitations is that response to treatment can sometimes be suboptimal, and underserved areas do not have access to more advanced therapies such as deep brain stimulation or botulinum toxin (Srinivasan et al., 2020).

In the case of Huntington's disease, telemedicine has proven to be helpful as mobility impairment and cognitive decline can be obstacles for in-person visits. It has been demonstrated that the reliability of motor assessments compared to in-person are sufficient (Bull et al., 2014) and in one study it was reported that telemedicine was being used by a quarter (23.6%) of the clinics surveyed (Frich et al., 2016). Nevertheless, there may be limitations when assessing subtle features such as saccadic eye movements or assessing tone and postural stability. There are, however, options regarding assessment of some of the nonmotor symptoms, for example, the written portions of the Montreal Cognitive Assessment are captured by a screenshot. Moreover, telemedicine can be helpful in facilitating genetic counseling to allow social workers to join the meetings from remote locations (Hawkins, Creighton, Ho, Mcmanus, & Hayden, 2013). Among the advantages of genetic counseling through telemedicine, patients have highlighted the importance of saving money and ease for other family members to attend.

As medicine is evolving, future neurologists should be aware of the value of telemedicine so they can continue enhancing the process and improving access to healthcare. A study was performed which included a teleneurology curriculum, and demonstrated an appreciation from neurology residents and better outcomes in medical education. Nevertheless, the participants agreed that it made it more difficult to establish a personal connection with the patients, so it cannot replace the in-person visits (Afshari, Witek, & Galifianakis, 2019). Advances in technology have enabled medical practice, research and education despite geographical barriers (Afshari et al., 2019; Ben-Pazi et al., 2018; Bull et al., 2014; Srinivasan et al., 2020).

Due to the complexity of movement disorders, interdisciplinary approaches are often necessary to develop optimal therapeutic plans for the patients. A study was done to identify the strengths and obstacles of a telepsychiatry program for patients with movement disorders, having a 96% visit completion rate, reducing caregiver burden, self-efficacy and social support (Seritan et al., 2019). Although more information is needed to evaluate the validity of these programs in other sociodemographic scenarios, it is valuable information so that they can be implemented in a standardized way in movement disorders programs around the globe.

Nothing will ever replace the power of the human touch in healing. Because of the advances in technology, virtual visits are not only possible but they are likely the wave of the future. Virtual visits are often preferred by patients not only because of convenience, but during the coronavirus pandemic, safety. Telehealth can ultimately lead to cost savings, more frequent patient-provider communication and potentially improved compliance with recommended care plans. As our world continues to evolve, we must maintain our flexibility and adaptability and remind ourselves that with change comes growth which may be difficult, but once adopted can improve access to high quality medical care.

References

1. Afshari, M., Witek, N. P., & Galifianakis, N. B. (2019). Education Research: An experiential outpatient teleneurology curriculum for residents. Neurology, 93(4), 170–175. https://doi.org/10.1212/WNL.0000000000007848
2. Albani, G., Ferraris, C., Nerino, R., Chimienti, A., Pettiti, G., Parisi, F., … Mauro, A. (2019). An integrated multi-sensor approach for the remote monitoring of parkinson's disease. Sensors (Switzerland), 19(21), 1–18. https://doi.org/10.3390/s19214764
3. Ben-Pazi, H., Browne, P., Chan, P., Cubo, E., Guttman, M., Hassan, A., … Spindler, M. (2018). The Promise of Telemedicine for Movement Disorders: an Interdisciplinary Approach. Current Neurology and Neuroscience Reports, 18(5). https://doi.org/10.1007/s11910-018-0834-6
4. Bull, M. T., Darwin, K., Venkataraman, V., Wagner, J., Beck, C. A., Dorsey, E. R., & Biglan, K. M. (2014). A Pilot Study of Virtual Visits in Huntington Disease. Journal of Huntington's Disease, 3(2), 189–195. https://doi.org/10.3233/JHD-140102
5. Cubo, E., Doumbe, J., López, E., Lopez, G. A., Gatto, E., Persi, G., & Guttman, M. (2017). Telemedicine Enables Broader Access to Movement Disorders Curricula for Medical Students. Tremor and Other Hyperkinetic Movements (New York, N.Y.), 7, 501. https://doi.org/10.7916/D8708CXW
6. Dorsey, E. R., Deuel, L. M., Voss, T. S., Finnigan, K., George, B. P., Eason, S., … Biglan, K. M. (2010). Increasing access to specialty care: A pilot, randomized controlled trial of telemedicine for Parkinson's disease. Movement Disorders, 25(11), 1652–1659. https://doi.org/10.1002/mds.23145
7. Frich, J. C., Rae, D., Roxburgh, R., Miedzybrodzka, Z. H., Edmondson, M., Pope, E. B., … Nance, M. (2016). Health Care Delivery Practices in Huntington's Disease Specialty Clinics: An International Survey. Journal of Huntington's Disease, 5(2), 207–213. https://doi.org/10.3233/JHD-160192
8. Group GBD 2015. (2017). Global, regional, and national burden of neurological disorders during 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. The Lancet Neurology, 16(11), 877–897. https://doi.org/10.1016/S1474-4422(17)30299-5
9. Hanson, R. E., Truesdell, M., Stebbins, G. T., Weathers, A. L., & Goetz, C. G. (2019). Telemedicine vs Office Visits in a Movement Disorders Clinic: Comparative Satisfaction of Physicians and Patients. Movement Disorders Clinical Practice, 6(1), 65–69. https://doi.org/10.1002/mdc3.12703
10. Hawkins, A., Creighton, S., Ho, A., Mcmanus, B., & Hayden, M. (2013). Providing predictive testing for Huntington disease via telehealth: Results of a pilot study in British Columbia, Canada. Clinical Genetics, 84(1), 60–64. https://doi.org/10.1111/cge.12033
11. Lei, C., Sunzi, K., Dai, F., Liu, X., Wang, Y., Zhang, B., … Ju, M. (2019). Effects of virtual reality rehabilitation training on gait and balance in patients with Parkinson's disease: A systematic review. PLoS ONE, 14(11), 1–17. https://doi.org/10.1371/journal.pone.0224819
12. Seritan, A. L., Heiry, M., Iosif, A.-M., Dodge, M., & Ostrem, J. L. (2019). Telepsychiatry for patients with movement disorders: a feasibility and patient satisfaction study. Journal of Clinical Movement Disorders, 6(1), 1–8. https://doi.org/10.1186/s40734-019-0077-y
13. Srinivasan, R., Ben-Pazi, H., Dekker, M., Cubo, E., Bloem, B., Moukheiber, E., … Guttman, M. (2020). Telemedicine for Hyperkinetic Movement Disorders. Tremor and Other Hyperkinetic Movements, 10, 1–8. https://doi.org/10.7916/tohm.v0.698
14. Wilkinson, J. R., Spindler, M., Wood, S. M., Marcus, S. C., Weintraub, D., Morley, J. F., … Duda, J. E. (2016). High patient satisfaction with telehealth in Parkinson disease A randomized controlled study. Neurology: Clinical Practice, 6(3), 241–251. https://doi.org/10.1212/CPJ.0000000000000252

A Case of Familial Hemiplegic Migraine Outside of Classic Diagnostic Criteria

Melissa Cook, MD
Jeffrey C. McClean II, MD, FAAN
Department of Neurology, San Antonio Military Medical Center, San Antonio, TX

INTRODUCTION

Familial Hemiplegic Migraine (FHM) is a disease process that classically involves a migraine headache with an aura of hemiplegia that is fully reversible. Additionally, the patient must have a first or second-degree relative that has identical attacks.[1] The disease process has an autosomal dominant mode of inheritance with reduced penetrance. Typical aura symptoms include visual, sensory, aphasic, and/or motor symptoms. In a study of a Danish population with FHM, most patients had more than two aura symptoms with 98% and 100% of the study population having motor symptoms and aphasic symptoms, respectively, resolving in less than 24 hours.[2] Rarely, migraine episodes can have prolonged auras of days to weeks and have associated fevers, meningismus, and impaired consciousness.[3] Patients typically have their first attack in the first or second decade of life and will have decreasing attack frequency with age.[2, 4]

FHM is classified into three types correlating with three genetic variants: CACNA1A, ATP1A2, and SCN1A. FHM type 1 (CACNA1A mutation) has been associated with progressive cerebellar symptoms ranging from nystagmus to ataxia which been found to be as prevalent as 20-50% in some studies.[2,3,4] Seizures have been reported more commonly in FHM type 2 (ATP1A2 mutation), but have been seen in population studies with FHM type 1.[2, 8] FHM Type 3 (SCN1A mutation) has also been associated with many epileptic syndromes. FHM, in general, is associated with many other headache syndromes, with Thomsen et al reporting 65% of their study population having one or two other migraine forms, which was seven times more often than expected when corrected for age and sex.[2] Recent data has suggested that the CACNA1A gene associated with FHM Type 1 is also involved in non-hemiplegic migraines and migraines with aura. It has been suggested that up to 10% of families with the pathogenic variant do not have hemiplegic migraines, but rather migraines with or without aura.[4]

Multiple studies have investigated the prevalence of electroencephalogram (EEG) abnormalities in migraine with aura and FHM. Some ictal abnormalities that have been recorded include spikes, sharp waves, slow waves, and increased photoparoxysmal responses. Sharps and spikes were the most common ictal phenomenon observed, possibly supporting the theory of temporal cortical dysfunction in migraines.[5] Multiple studies have also demonstrated EEG abnormalities during headache free periods in migraineurs with or without aura.[5,6,7] Diffuse slowing was the most frequent interictal phenomenon and the most common location for any abnormality was the occipital region.[5] A study by Bjork found that globally increased theta activity was the most common interictal finding in patients with migraines and that theta activity would significantly increase prior to a headache attack.[6] It was postulated in this study that these pathological theta rhythms were due to reduced cerebral blood flow in the grey matter as seen in other disease processes such as cardiovascular disease, dementia, and encephalopathies.

We describe a case of an atypical presentation of familial hemiplegic migraine with a predominant aphasic aura with abnormal ictal and interictal EEG findings.

CASE REPORT

A 24-year-old Caucasian male military recruit with no known medical history presented to the emergency department for global aphasia, appendicular ataxia, and the inability to walk. Initial history obtained from collateral sources included a sudden-onset headache and visual deficits about one hour prior to presentation. Additional history was notable for possible recent excessive alcohol use, but otherwise unremarkable for recent travel, exposures, drug use, or sick contacts. Upon examination, the patient was alert but following only intermittent simple visual commands with an inability to understand vocal commands or produce comprehensible words. The remainder of the exam was limited by aphasia, but no focal weakness or hemiparesis was evident. A non-contrasted CT scan of the head and initial lumbar puncture were unremarkable, including HSV PCR. An EEG showed continuous rhythmic slowing in the left greater than right frontal regions with an intermittently present posterior dominant rhythm on the right. (Figure 1). He was started on empiric antibiotic and antiviral coverage for meningitis and encephalitis without steroids and admitted to a medical telemetry floor.

Patient developed a fever to 102.9 F within hours of hospitalization and a leukocytosis (14,700 cells/mm^3 with 85% neutrophils) on hospital day two; both were transient and resolving by day three. A contrasted MRI of the brain was unremarkable, without evidence of encephalitis, meningeal enhancement, or any other abnormalities.

During the hospitalization, further history was obtained from the patient's out of state family. The patient's father reported a personal history of genetically confirmed (CACNA1A) FHM type 1, characterized by episodes of unilateral paresthesia, weakness, incoordination, and aphasia lasting minutes to hours provoked by stress as well as a similar syndrome in the patient's paternal grandfather. Interestingly, there was no report of fever associated with these episodes. Both family members were treated with a calcium channel blocker as prophylaxis.

Gradual improvement was observed over several days to include improved speech fluency and ability to follow complex commands. As the aphasia resolved, he was able to also report the presence of prominent paresthesias on the right side. On hospital day five a repeat contrasted MRI brain and lumbar puncture were again unremarkable. Empiric coverage for bacterial etiologies was discontinued and status migrainous treatment was started with intravenous chlorpromazine and magnesium. Empiric

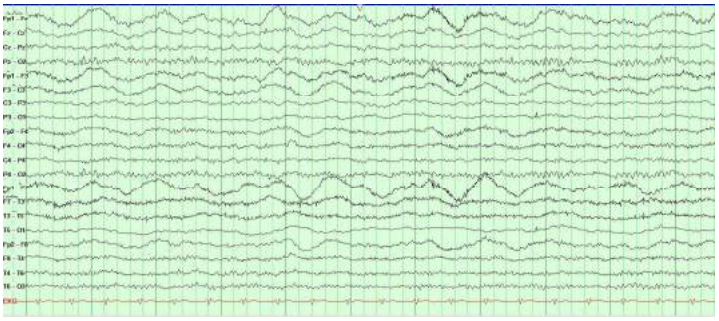


Figure 1. Initial EEG – This recording was notable for continuous rhythmic slowing in the left greater than right frontal regions. The background on the right had preserved organization with a PDR of up to 12.5 Hz which was appropriately reactive.

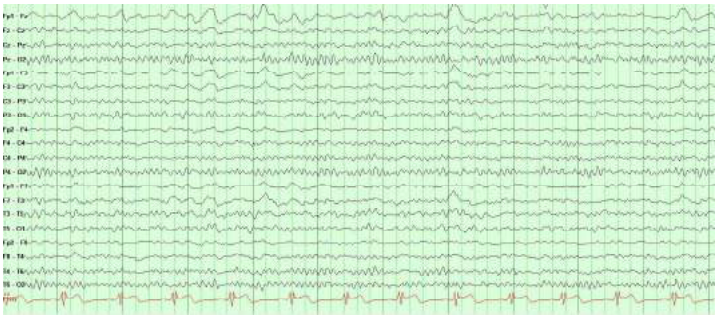


Figure 2. Follow-up EEG one month after complete resolution of symptoms. Single slow waves and bursts and trains of 2-5 Hertz delta and theta activity occur intermittently in the left frontal, temporal, and central derivations during wakefulness and drowsiness. It is associated with loss of faster frequencies that are recorded at the same time in homologous derivations on the right.

coverage for viral encephalitis was discontinued after a second normal HSV PCR.

At discharge on hospital day eight, the patient still had mild word finding difficulties with resolution of all other symptoms. During outpatient follow-up after complete resolution of the inciting event without repeat headache symptoms, serial EEGs were performed that showed varying amounts of focal left frontal-central-temporal dysfunction, a month after the initial attack (Figure 2). The patient reported a personal history of mild migraine headaches and a single episode at the age of 18 of unilateral paresthesia and headache lasting approximately 30 minutes. Genetic testing confirmed a mutation of the CACNA1A gene (Exon 17, VAL715ALA). The patient was started on verapamil for migraine prophylaxis. At eighteen months after initial presentation, the patient remains on prophylaxis and free of recurrence.

DISCUSSION

Familial Hemiplegic Migraine is a migrainous disorder associated with an aura of hemiplegia and a visual, sensory, or aphasic aura that is fully reversible as well as a family history of similar attacks. Despite these well-defined criteria, the diagnosis of hemiplegic migraine can be challenging during acute evaluation. Our patient's predominant symptoms were aphasia and sensory complaints, with mild motor and visual deficits. Additionally, he mounted a fever and leukocytosis with a corresponding EEG showing significant hemispheric dysfunction, most concerning for encephalitis at initial presentation. His headache treatment was delayed given his clinically objective findings, inability to convey personal and family history, and supportive data (lumbar puncture, EEG, and MRI) that did not lead to a congruent diagnosis. With intravenous treatments for migraine, his symptoms gradually improved and he has not had another migraine attack since initiation of prophylactic therapy after eighteen months.

Our patient's presentation differed from the typical course of FHM, specifically his type of predominant aura, length of the aura, and ictal and interictal EEG dysfunction. In the Danish population study previously mentioned, only 59% of patients had true hemiplegic motor symptoms, while 41% presented with non-hemiparetic symptoms.[2] This interesting observation is incongruent with the current definition of the ICHD-3 criteria requiring hemiplegia for the diagnosis. However, the criteria does acknowledge that weakness may be difficult to distinguish from sensory loss, which may be the case for our patient given his minimal motor complaints. The length of his aphasic aura symptoms was much longer than previously reported values, improving slowly over more than a week, but sensory and motor deficits resolved within typical norms of 72 hours. This raises further questions about the length of time allowed for resolution of symptoms in the current criteria. Lastly, the patient had not only ictal findings, but interictal findings on EEG that were present over a month after complete resolution of his symptoms. Given the patient's presentation, this provides further evidence that clinicians need to have a low threshold to include migrainous disorders in the differential diagnoses for similar presentations, even if the diagnostic criteria are not perfectly met. This case is example of an atypical presentation that further highlights the phenotypic variability of the group of genetic disorders labeled hemiplegic migraines.

References:

1. Headache Classification Subcommittee of the International Headache Society. *The International Classification of Headache Disorders*. 2 ed. *Cephalalgia*. 2004; 24:9–160.

2. Thomsen LL, Eriksen MK, Roemer SF, et al. A population-based study of familial hemiplegic migraine suggests revised diagnostic criteria. *Brain*. 2002; 125(6):1379-1391.

3. Silberstein SD, Lipton RB, Dalessio DJ, editors. *Wolff's headache and other head pain*. 7th ed. New York:Oxford University Press, 2001, pp.132-133.

4. Ducros A, Denier C, Joutel A, et al. The clinical spectrum of familial hemiplegic migraine associated with mutations in a neuronal calcium channel. *New England Journal of Medicine*. 2001; 345(1):17-24.

5. Ozkan M, Teber ST, Deda G. Electroencephalogram variations in pediatric migraines and tension-type headaches. *Pediatric neurology*. 2012; 46(3):154-7.

6. Bjørk MH, Stovner LJ, Engstrøm M, et al. Interictal quantitative EEG in migraine: a blinded controlled study. *The journal of headache and pain*. 2009; 10(5):331-9.

7. Chastan N, Lebas A, Legoff F, et al. Clinical and electroencephalographic abnormalities during the full duration of a sporadic hemiplegic migraine attack. *Neurophysiologie Clinique/Clinical Neurophysiology*. 2016; 46(4-5):307-311.

8. De Fusco M, Marconi R, Silvestri L, et al. Haploinsufficiency of ATP1A2 encoding the Na+/K+ pump alpha2 subunit associated with familial hemiplegic migraine type 2. *Nat Genet*. 2003; 33:192–196.

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Medical Cannabis In Texas – Past, Present and Future

Dr. Karen Keough, Board-Certified Child Neurologist & Epileptologist and Chief Medical Officer, Compassionate Cultivation

Every practicing neurologist faces questions from their patients about medical cannabis. Since February 2018, when the first prescriptions were filled under the Texas Compassionate Use Act, we have learned much about its potential clinical benefits and how best to integrate it into patient care. As an early adopter of medical cannabis therapy for my patients with refractory epilepsy, and now for patients with autism and spasticity, I'd like to share some of that experience in hopes that more patients will gain access to this important therapeutic option.

In this review, I will provide some basics about medical cannabis, share salient published evidence for its efficacy and safety, and summarize my own experience with 135 patients who have undergone cannabis therapy. I will then touch on the expansion the Texas Compassionate Use Act in June 2019 that now includes several new conditions, most of them relevant primarily to neurologists.

Medical Cannabis and its Two Key Compounds, CBD and THC

The human endocannabinoid system (ECS) was discovered in the 1990s during research on the effects of cannabis on the human body. Two cannabinoid receptors (CB1 and CB2) have been discovered. Both moderate a wide range of systems including memory, mood, motor function and pain perception and immune function. CB1 receptors are found mainly in the brain and central nervous system; CB2 receptors, in the immune system. Cannabis plants produce a thick substance containing over 100 different cannabinoid compounds. The most common cannabinoid compounds are CBD (cannabidiol) and THC (tetrahydrocannabinol). Hemp is a subtype of cannabis that contains low concentrations of THC, a distinction relevant to laws related to agriculture and commercial sales of cannabis products.

A Brief History of Cannabis as Medicine

Used medically for centuries, cannabis was first described in the United States Pharmacopoeia in 1850. Its use and sale were federally restricted for the first time in 1937 under the Marihuana Tax Act. In 1942, it was removed from the United States Pharmacopoeia. The passage of various laws in the 1950s and the Controlled Substances Act of 1970 effectively criminalized cannabis use and possession and limited research on it.

In 1996, through its Compassionate Use Act, California became the first state to sanction access to and use of botanical cannabis for medicinal purposes with authorization by a physician. By January 2019, 36 states, the District of Columbia, Guam, and Puerto Rico had enacted legislation governing medicinal cannabis sale and distribution; 21 states and the District of Columbia had decriminalized marijuana possession in small amounts, and nine states (Alaska, California, Colorado, Maine, Massachusetts, Michigan, Nevada, Oregon, and Washington) and the District of Columbia had legalized adult recreational use of marijuana. Each state can define its own medical cannabis program, so definitions vary widely. Texas defines medical cannabis as "low-THC" cannabis derived from *Cannabis sativa* or any derivative that contains no more than 0.5% tetrahydrocannabinol (THC).

The Texas Compassionate Use Act

Originally passed in June 2015, the Texas Compassionate Use Act allowed the creation of a system for physician prescription of high-CBD, low-THC medical cannabis exclusively for the treatment of refractory epilepsy. In February 2018, the first Texas dispensary (Compassionate Cultivation) opened in Manchaca, just south of Austin. One of only three licensed dispensaries in the state at the time, it officially began producing, processing, and distributing the only authorized formulation at the time: a 20:1 ratio of CBD-to-THC in compliance with the state's maximal concentration of THC (0.5%) and minimal concentration of CBD (10%). This formulation became known as Lonestar CBD.

Experience with 20:1 traditional Lonestar CBD

The choice of refractory epilepsy as the first target for medical cannabis therapy in Texas was prescient. Between 2017and 2018, three landmark publications confirmed the safety and efficacy of high CBD therapy for prevention of seizures in patients with complicated refractory epilepsy. [1,2,3] These studies supported the long-held expectations of many patients that medical cannabis in the form of cannabidiol could provide benefit in the most challenging cases. These studies also identified potential side effects and gave important insight into relevant dosages. Although generalization of these data to artisanal CBD therapy is fraught with unwarranted assumptions, these early studies provided a foundation for prescribing empiric CBD/THC therapy to patients with refractory, life-threatening seizures. Meanwhile, the establishment of highly regulated state-sanctioned CBD dispensaries provided a safe, reliable source of therapeutic CBD. Subsequently, my partners and I are conducting an IRB-approved observational study of CBD treatment in 135 patients with complex refractory epilepsy from February 2018 to January 2020. (see Figure 1)

Here are the most important lessons I have learned:

1. For some patients, CBD is the best thing they have ever tried for epilepsy.

   Four of my patients (3%) on empiric monotherapy with CBD or CBD/THC are now seizure-free. All four had previously failed to achieve seizure control on 3-5 trials of other seizure medications. These cases of children with severely refractory epilepsy now fully controlled by the empiric use of one medication highlight the importance of a trial of CBD therapy in highly refractory patients.

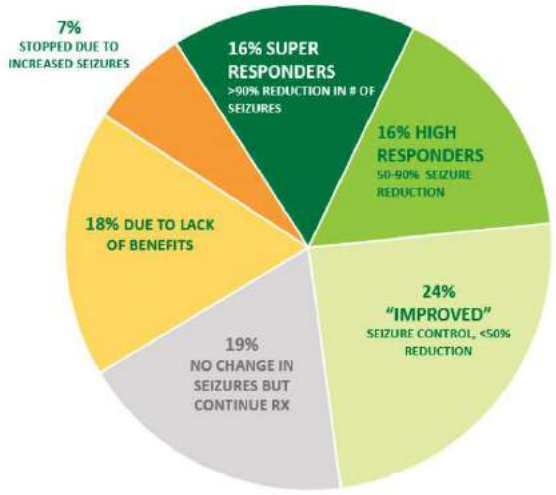


Figure 1: 135 patients treated with Lonestar CBD 20:1 formulation with or without Epidiolex February 2018 – January 2020. Duration of follow-up ranged from 1 month – 22 months.

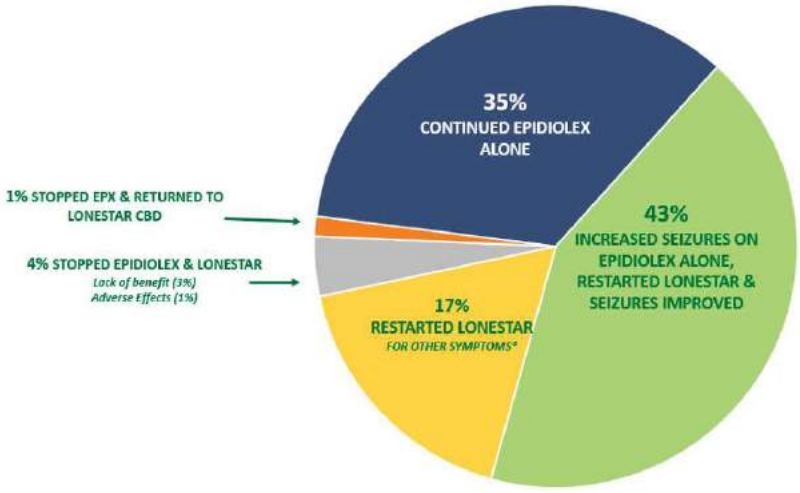


Figure 2: 75 patients who took 20:1 Lonestar CBD & transitioned to Epidiolex therapy. Duration of follow-up ranged from 2 – 24 months.

2. Seizure-freedom is not the sole measure of success.

   Because the original Compassionate Use Program in Texas was restricted to patients with refractory epilepsy, every patient in our trial had failed at least 2 prior trials of seizure medication, and often several more. Kwan and Brodie's landmark study famously demonstrated the challenge of achieving full seizure control in a refractory population.[4] Decreasing seizure frequency and severity with minimal side effects are realistic and vital goals of treatment. In my series, 32% of patients achieved >50% seizure reduction during a follow-up period of 1-22 months (>6 months in 78 patients). An additional 24% reported a worthwhile reduction.

3. CBD therapy may exacerbate seizures. This was observed in the Epidiolex trials as well. Although relatively infrequent (7% in my series), I verified this outcome by a second trial in several of these patients. A few other patients responded well at low doses, had more seizures at higher doses, and then improved when the CBD dose was decreased.

4. Most of my patients (75%) retain CBD as part of their treatment regimen.

   For most patients, the combination of improved seizure control and a beneficial profile warrant continued use of CBD. CBD not only has few adverse effects, but many parents and patients report improved alertness, responsiveness, and expressive language. These reports are difficult to quantify and may in part represent placebo effects. However, unlike most of my follow-up conversations with patient and families about other medical therapies, conversations about CBD usually focus on "what else is better", instead of what is "new and worse". One powerful demonstration of CBD's beneficial impact is that many patients continue using it, despite the considerable out-of- pocket cost of dispensary CBD/THC to their families.

5. THC contributes independent benefits compared to CBD alone. Because the Texas Compassionate Use Act allowed for initiation of therapy in February 2018, and Epidiolex was not widely available until a year later, 75 patients in this series had long-term therapy with dispensary CBD before switching to Epidiolex therapy. Figure 2 shows the response of patients switched from dispensary Lonestar CBD to Epidiolex. For some patients, the change was unremarkable. In other patients, the ability to use higher doses (because insurance covered the cost of Epidiolex) resulted in improved seizure control. However, in 43% of patients, seizures increased in those who had achieved better control on dispensary CBD. In another 17% of cases, new side effects appeared that had not been seen before switching to Epidiolex. In both of these groups, the reinstitution of THC therapy in combination with Epidiolex alleviated these problems. I now treat many patients with a combination of low-CBD (balanced formulation) Lonestar CBD with Epidiolex. I now transition this way proactively by converting high-CBD treatment to balanced formulation when I add Epidiolex. To better understand this combination, please read the next portion of the article regarding the expansion of the Texas Compassionate Use Act that resulted in new formulation options in Texas. Prescribing THC to children understandably raises concerns about adverse effects. According to data that come mainly from studies of recreational drug use or animal models, learning, memory, and attention may be impaired after recent cannabis use (within 24 hours) and even after cannabis use is discontinued. Cannabis abuse may increase the risk of schizophrenia and other psychoses, and use of THC at higher concentrations has been associated with greater risk in population studies.[5] Although these risks are related to dose, what a "safe" dose is remains unknown. Moreover, differential risk in developing brains has not been extensively studied. Therefore, I discuss these concerns with all

my patients and their parents before initiating CBD therapy. How the short- and long-term risks of CBD/THC therapy compare with the risks of treatment with standard prescription medication are also unknown. However, given the serious symptoms and diagnoses that inspire these families to explore CBD/THC treatment in the first place, most patients and caregivers are willing to accept these risks.

Expansion of the Texas Compassionate Use Program (T-CUP).

In June 2019, based on the success of the intractable epilepsy program, the T-CUP was expanded, allowing medical cannabis treatment for a broader set of qualifying conditions, including:

- all forms of epilepsy and other seizure disorders
- autism
- multiple sclerosis
- spasticity
- amyotrophic lateral sclerosis
- terminal cancer
- other neurodegenerative disorders such as Alzheimer's and Parkinson's disease, and many more as defined in a list from the Texas Department of Health and Human Services. https://texreg.sos.state.tx.us/public/readtac$ext.TacPage?sl=R&app=9&p_dir=&p_rloc=&p_tloc=&p_ploc=&pg=1&p_tac=&ti=25&pt=1&ch=1&rl=61

Discussion of approach to treatment for these many conditions is beyond the scope of this article, though I will expand on treatment for autism below. For more extensive references on medical cannabis in the treatment of these conditions, Compassionate Cultivation has compiled a complete repository of condition-specific medical studies on their website (www.texasoriginalcc.com).

Other important changes in the T-CUP included:

1. removing the requirement for a second qualified medical opinion,
2. eliminating the 10% 'floor' for CBD content in products. The latter change allowed T-CUP dispensaries to offer a variety of THC:CBD ratios that target other symptoms that benefit from lower CBD:THC ratios--symptoms such as pain, muscle spasms/spasticity, lack of appetite, insomnia, restlessness and others.

Understanding Ratios and Formulations

Medical cannabis can produced in various formulations with differing ratios of CBD and THC. However, the maximum concentration of THC remains limited to 0.5% THC by weight. A useful clinical distinction is comparing high-CBD formulations with balanced (low-CBD) formulations. All formulations of Lonestar CBD have the same state-mandated maximum THC concentration of 0.5%. High-CBD formulations contain up to 20 times the concentration of CBD compared to THC. This includes the original version of Lonestar CBD with a 20:1 ratio: 100 mg/mL CBD + 5 mg/mL THC. Clinical research suggests that in addition to providing a positive impact on seizure control, high-CBD formulations can alleviate some symptoms associated with autism such as anxiety, depression, restlessness and disruptive behavior.

Balanced formulations have similar levels of CBD and THC by weight. Lonestar CBD is also available in 3:1 ratio (15 mg/mL CBD + 5 mg/mL THC) and 1:1 ratio (5 mg/mL CBD + 5 mg/mL THC). Clinical research suggests that balanced formulations can have a positive impact on symptoms associated with T-CUP qualifying conditions such as terminal cancer, autism and other neurodegenerative disorders, as illustrated in the chart in Figure 3. Some patients may experience multiple symptoms that could respond to either high-CBD formulations or balanced formulations, or a combination of both. I utilize the 1:1 Lonestar formulation frequently in combination with Epidiolex, which has no measurable THC content, to enhance seizure control and to mitigate other symptoms that may be present prior to treatment or that may be provoked by high-CBD therapy, such as insomnia, anorexia, and agitation.

How Does a Doctor Register to Prescribe Medical Cannabis in Texas?

Joining the Compassionate Use Registry is simple: visit the Texas Department of Public Safety Compassionate Use Registry portal at https://curt.dps.texas.gov/app/application/physicianEmailInvitation.xhtml.

Enter your name and email address – an email including a link to the Physician Registration Wizard will be sent to you. To register, you will need 1.) the Texas Medical Board License number, 2.) your American Board of Medical Specialties number and 3.) your Texas Driver's License audit number. After completing the application, you will receive a confirmation email and tracking number. Note that verification by the Department of Public Safety can take between 1 – 10 business days. Originally, all physicians who registered were listed on the CURT website, but now listing is optional. Physicians must expressly provide consent in order to be listed.

How Should a Physician Approach Dosing?

Like most new medications, dosage recommendations for cannabis medicines are best established according to existing scientific research, careful integration of high-quality anecdotal evidence, and repeated evaluation of individual patient outcomes. The process of finding the correct dose differs for each patient, determined through an empiric titration process. The dosing strategy of cannabidiol starts at 5 mg/kg/day, targeting 10 mg/kg/day and ranging up to 20 mg/kg/day or higher. These doses are not sustainable financially for most adult patients, though smaller children can reach high per-kilogram dosing at affordable rates. In my series of epilepsy patients utilizing 20:1 Lonestar CBD, many patients achieved improvement in seizure control at much lower doses than suggested in the Epidiolex trials. I start with a dose of 0.5 mg/kg/day (minimum dose 5 mg = 0.05 mL) and titrate weekly. Most patients did well on 3-8 mg/kg/day. Some went higher than 10 mg/kg/day and this can achieve better results in some patients, but cost can be limiting. The ability to achieve higher CBD dosing through insurance approval of Epidiolex is game-changing for some of my pa-

Compassionate Cultivation

	APPROVED CONDITIONS				
Symptoms	EPILEPSY	AUTISM	MS/SPACTICITY	TERMINAL CANCER	ALS
Anxiety	High-CBD		High-CBD	High-CBD	
Depression		High-CBD			
Seizures	High-CBD	High-CBD			
Restlessness		High-CBD			
Disruptive Behavior		High-CBD			
Pain			Balanced	Balanced	Balanced
Appetite Loss				Balanced	Balanced
Spasticity			Balanced		Balanced
Insomnia				Balanced	
Nausea				Balanced	
Neuropathic Pain			Balanced		
Tics		Balanced			

Patients taking concomitant medications should start at the lower dose and titrate more slowly. Medications metabolized by liver enzymes or highly protein-bound in the blood should be considered and titrated slowly. Some may require measurement of serum drug levels after starting CBD to allow further adjustment.

Higher doses than these have been utilized in some clinical trials but may not be necessary in all patients to achieve good results. These higher doses may be well tolerated, but we need more experience with this product to understand the range our patients need for optimal response with minimal side effects.

Figure 3. This table summarizes various studies differentiating the effects of CBD/THC formulations based on symptoms. Often the target symptom of therapy is more useful than the qualifying diagnosis when choosing the right ratio of CBD:THC for treatment.

tients. I always seek Epidiolex approval in patients who have demonstrated a response to CBD therapy. This has become increasingly successful as Epidiolex has had more time on the market and insurers recognize that some patients benefit remarkably well in off-label use.

Dosing balanced formulations: THC is far more potent for producing a clinical effect per milligram compared to CBD. Whereas patients utilizing high CBD treatments will take doses in the hundreds of milligrams per day, THC can have clinical impact with only a few milligrams per day. CBD is included with THC in the balanced formulation intending to mitigate some of the concerning effects of THC, including euphoric effect, and risk of psychosis. The ideal combination of CBD and THC is not well understood and is likely to vary depending on the targeted symptoms and/or individual patient responses. Dosing balanced formulations is best conceptualized as primarily dependent on the THC component. Variation of 1 or 2 milligrams/day can have a differential impact. The amount of THC that may impart a euphoric effect is not clearly determined but may be as low as 5 mg without CBD in the mix. Doses above 10 mg at a time or above 20 mg/day should be considered with caution. Clinical studies show the starting dose of balanced formulations for most targeted conditions/symptoms will range from 2.5-5mg of THC per day, and lower in smaller patients. This guidance is especially important when initiating therapy for patients with no prior experience using cannabis medicine. Medically sensitive and complex patients, such as young children or those taking multiple concomitant seizure medications, should be started at a lower dose and titrate more slowly. Less sensitive patients can be started at a somewhat higher initial dosage.

For optimal delivery of medication, it should be placed inside the mouth between the cheek and gums or on the tongue and allowed to be absorbed. Compassionate Cultivation offers a spray formulation of the 20:1 formulation that optimizes mucosal absorption. The medication can be swallowed rather than absorbed in the mouth, but less medication will reach circulation due to first-pass hepatic metabolism.

AUTISM

The expansion of eligible conditions by Texas House Bill 3703 in June 2019 added autism to the list of eligible conditions for the Texas Compassionate Use Program. Studies examining CBD/THC therapy for autism are much smaller than studies of epilepsy patients, and they are observational without placebo controls. Several larger scale phase III randomized placebo-controlled trials are underway internationally, but those results are still unknown. Poleg et al published a useful

review or articles addressing CBD therapy for autism in 2019.[6]

True to its name as a spectrum disorder, autism can manifest with mild to severe behavioral symptoms that often prove difficult to manage pharmacologically. These challenges motivate patients and caregivers to seek alternatives that might improve efficacy, mitigate side effects, or both. Published studies of patients with autism suggest benefits from CBD in alleviating anxiety, attention, hyperactivity, impulsivity.[7] THC has more beneficial impacts on insomnia and aggressive behavior. In my experience, the essential role of THC in managing these challenging symptoms frequently manifests itself when patients convert from Lonestar CBD to Epidiolex, which does not contain any THC but only CBD. These are the two most common symptoms other than increase of seizures that have led me to restart or maintain THC as part of the treatment regimen when patients transition to Epidiolex. Because of the apparently complementary effects of CBD and THC, they are "good partners" in therapy. Finding the right ratio of CBD and THC in combination for individual symptoms, conditions and patients is an empiric process, since studies assessing various ratios are not available for guidance. The evidence-base to guide CBD/THC treatment of autism will expand considerably soon with the expected conclusion and publication of several larger, placebo-controlled trials underway involving CBD and CBDV (another cannabinoid not yet in wide clinical use) as mentioned in the Poleg article.

TERPENES AND "WHOLE PLANT" FORMULATIONS

Terpenes are chemicals found in plants that create aromas or flavors. Any given terpene can be found to exist in a variety of different plants. For instance, α-Pinene is found in pine needles. Linalool is found naturally in lavender. ß-Caryophyllene is found in black pepper, cloves, rosemary and hops. Limonene is common in citrus fruit. Many terpenes exist in cannabis, and the mixture depends on the individual plant. Because the plants grown at the dispensary are clones, their terpene profile is uniform. There is much speculation about the role of terpenes as a contributor to the therapeutic effects of medical cannabis treatment, referred to as the "entourage effect". Although health implications have been attributed individually to many terpenes, the studies supporting these association generally were derived from animal models[8], and no human studies have carefully examined the entourage effect. Many patients express interest in CBD/THC preparations that include terpenes. At Compassionate Cultivation, the "Plus" formulation of each product contains the standard mixture of terpenes that is derived from their stock plant and is a consistent additive between batches. I have a few patients who utilize the Plus form at their request. I have not had any patients display a clear difference with the addition of terpenes, but only a few of my patients have requested it. Other artisanal CBD suppliers offer "whole plant" formulations that include both terpenes and also a mixture of other cannabinoid compounds that are extracted along with CBD and THC when the plants are processed. This complex mixture is highly variable when sourced from producers who have varied *cannabis* sources. Several cannabinoids have become the focus of early studies seeking additional clinical applications for medical cannabis. As a prescriber, I prefer a pure preparation without terpenes or other cannabinoids, so that I have a full understanding of what the patient is taking and I can guide therapy within the context of established evidence regarding the effects of CBD and THC. Other prescribers have shared with me that their review of evidence on the impact of terpenes and other cannabinoids supports some expectation of additional benefits. I encourage prescribers to become informed about these issues, because patients often have read a lot about the topic and will ask for opinions.

Where Can I Learn More About Prescribing Medical Cannabis in Texas?

Compassionate Cultivation has compiled an excellent repository of research on medical cannabis as it relates to the conditions approved by the Texas legislature can be found at the Compassionate Cultivation website: https://texasoriginalcc.com/conditions-symptoms/. For more information, contact the dispensary at (512) 614-0343.

Dr. Karen Keough is a board-certified pediatric neurologist who specializes in treating intractable epilepsy at Child Neurology Consultants of Austin. She serves as Chief Medical Officer of Compassionate Cultivation. She initiated the child neurology residency program at Dell Medical School at the University of Texas at Austin and continues to serve as faculty.

References:

1. Devinsky et al, Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. **N Engl J Med** 2017; 376:2011-2020
2. Thiele et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. **Lancet.** 2018 Mar 17;391(10125):1085-1096.
3. Devinsky et al, Effect of Cannabidiol on Drop Seizures in the Lennox–Gastaut Syndrome **N Engl J Med 2018**; 378:1888-1897
4. Kwan P, Brodie MJ. (2000) Early identification of refractory epilepsy. **N Engl J Med** 342:314–319.
5. The Health Effects of Cannabis and Cannabinoids: the current state of evidence and recommendations for research. National Academies of Science, **Engineering and Medicine**, 2017. Nationalacademies.org/CannabisHealthEffects.
6. Poleg et al. Cannabidiol as a suggested candidate for treatment of autism spectrum disorder. **Progress in Neuropsychopharmacology & Biologic Psychiatry** 89 (2019) 90-96
7. Schleider et al. Real Life Experience of Medical Cannabis Treatment in Autism: Analysis of Safety and Efficacy. **Scientific Reports** 2019 9:200.
8. Koziol A et al. An Overview of the Pharmacological Properties and Potential Applications of Natural Monoterpenes. **Mini-Reviews in Medicinal Chemistry** 2014, *14*, 1156-1168

Understanding Business and Neurology

Eddie L. Patton Jr., MD, MBA, MS, FAAN

Neurology training at Baylor College of Medicine prepared me with the skills to evaluate and diagnose complex neurological cases. I vividly remember my first time in the hot seat during "Appel Rounds" which was a weekly patient case presentation hosted by Dr. Stanley Appel. Each PGY2 was indoctrinated into residency by sitting in the front of a room, next to an empty chair surrounded by fellow residents. The chair next to you was soon filled by a selected patient. The senior residents taking their position toward the back trying to stay as far away from the line of fire as possible. It was the resident's job to interview the patient, examine him and come up with a diagnostic plan and differential diagnosis. The patient approached, I shook his hand and introduced myself. He introduced himself and sat down. At that point, Dr. Appel asked me, what was my diagnoses. As sweat started to gather across my brow I could see the senior residents trying to hold back their laughter. In my nervous state I failed to pay close attention to the frontal balding, temporal muscle wasting, or the prolonged amount of time it took the patient to let go of my handshake. Since then, I would like to think that I have not missed another case of myotonic dystrophy. Situations like this prepared me to be clinically thorough, but the one area I wish I would have had additional training in was how to bill for this encounter. Should I bill for the time of the visit or the complexity of the case?

In an academic or training environment, the number of cases one saw per day was emphasized in order to give the best clinical exposure rather than teaching about the number of patients needed to be seen to generate revenue. There the focus was on taking the time to properly diagnose complex neurological cases, rightfully so. However, so many questions ran through my mind as I was completing training. How do procedures like EMG/NCS or EEGs increase profitability or marketability? Should I go into solo practice, group practice, stay academic, or join a large physician organization? When does one consider incorporating Advanced Practice Provider's (APPs)? It wasn't until the final months of my neuromuscular fellowship that I was exposed to certain business principles that would later have a huge effect on my practice decisions. That was when I had my first employment contract to review. After reading it a few times I realized, it would be best to have a lawyer review my contract. Needless to say, there were other residents in similar situations. This is when I realized if I wanted to succeed in practicing neurology and be an effective patient advocate, I needed to understand not only the profession of neurology but the business of medicine.

There are neurological and medical conferences to help strengthen our clinical acuity but there aren't a lot of resources that help us learn about the business side of medical practice. This led to the creation of the informational video series produced by the Texas Neurological Society called "The Business of Neurology". The initial videos included pieces on contract negotiation, coding and billing, enhancing practice through ancillary services, and advanced practice providers. In response to the CoVid19 pandemic, a series was added on telemedicine.

CONTRACT NEGOTIATION

Contract negotiation is an essential skill that physicians must learn considering the changing healthcare landscape. Attorney, Bill Small of Houston, Texas was interviewed about contract negotiation and drew upon his 40-year history of healthcare law to shed some insight into the things to look out for. Why is it important to have an attorney review your contract? The short answer is there are certain traps that can be avoided if you have your contract reviewed by an attorney that has experience in healthcare. Attorneys specialize in different areas just as physicians do. Healthcare employment contracts are like no other industry, so it is important that you seek council from someone who has experience in reviewing these contracts.

Having an attorney review your contract could cost anywhere from a few hundred dollars to a couple of thousand dollars depending on the complexity of the contract and the attorney used. But, realize there is a risk that you are mitigating in spending this amount up front. If your contract being negotiated is a three-year contract for $150,000 per year, the total value of that contract could exceed well over half a million dollars when you include benefits, bonuses and extras such as travel and conference reimbursements. It is worth making the initial investment considering the long-term implications of the contract.

Other key aspects include duties and responsibilities, termination clauses, non-complete clauses, and productivity clauses. The non-compete clauses tend to be a hot button in negotiations. The non-compete clause restricts an employee, once terminated or if they leave an employer, from doing the same thing within a determined geographical area and for a certain time frame. For physicians non-compete clauses are not considered restriction of trade. Fighting these clauses after they are enforced can be expensive and time consuming. It is much better to negotiate this on the front end. If your position is strong, you can minimize the proposed distance or time as much as possible. You can negotiate this out of the contract all together. According to Bill Small, "The ability to negotiate comes down to how bad you want this job or how bad they want you".

RUN YOUR PRACTICE OR YOUR PRACTICE WILL RUN YOU

Healthcare is changing rapidly and as clinicians we are constantly under pressure to do more in less time. Reimbursements are changing and we must adapt to a world of increased regulatory and administrative burden. But the end result is the same. We all desire financial stability, work satisfaction and a work-life balance. This desire seems to be drifting farther and farther

away. One way to try and catch up to this desire is to understand more of what drives the economics of the practice of medicine.

In this project, David Evans, Chief Executive Officer of Texas Neurology shared his insight on how to incorporate more services into a neurology practice. We should embrace the fact that health technology is integrating into what we do every day in treating patients. There are ways that we can use technology to make things faster and decrease the administrative burden that we face. From using kiosk to facilitate patient check in's to providing telemedicine services to carrying out patient visits, information technology is making its way into our practices. The question for many neurologists is how and when to add ancillary services. This comes down to a business decision. After analyzing the economics of acquiring a product or service you can determine if that investment is best for your practice.

TELEMEDICINE

The coronavirus pandemic fast-forwarded the telemedicine industry by a number of years. Telemedicine was still in its infancy prior to CoVID19. Legislative changes in several states, including Texas, were making this addition to your practice more appealing, but low reimbursement did not make it a gamechanger. Then came the coronavirus pandemic and with it the practice of social distancing. Clinic volumes decreased almost overnight. This public health crisis brought with it a financial crisis that has touched every aspect of our society, including healthcare.

In his video interview, Dr. Eric Anderson, a pioneer in neurology telemedicine shared his insights on this growing industry. This technology allows us to keep seeing patients while practicing the social distancing practices that will ultimately slow the spread of the virus. In addition to that, state governors and the federal government made the popular decision to reimburse some telemedicine codes at the same rate as in person office visits. This was a savior for some practices, but not all. Rules were eased allowing physicians to use non-HIPPA compliant software like FaceTime and Zoom, but this was still a huge adjustment. Nevertheless, there was growing confusion surrounding coding that slowed adoption for some. Today many state and national organizations are providing resources to help physicians navigate this unfamiliar landscape. But is it enough? The future of telemedicine and how it will be incorporated into practice is still in question. Neurologists across the nation have used this time of loosened regulatory requirements and better reimbursements to test the waters. Telemedicine may or may not be for you. However, a better understanding of the finances surrounding the addition of this technology and new way of taking care of patients allows you to make a more informed decision.

INCORPORATING ADVANCED PRACTICE PROVIDERS

Another business aspect of neurology that has growing popularity is when and how to incorporate advanced practice providers (APPs). The term is used to encompass both nurse practitioners and physician' assistants, but a brief look at their history will show that they are two are very distinct professions. I sat down with Dr. Stuart Black, Texas Neurological Society board member who has over 20 years of experience in working with and training APP's. He gave an interested overview on this topic. Both groups were founded around the same time to address the problem of primary care physician shortages. On July 30, 1965 President Lyndon B Johnson signed Medicare and Medicaid into law. There was already a shortage of physicians but now with Medicare and Medicaid in effect, this made the problem worse. Dr. Eugene A. Stead Jr., chair of internal medicine at Duke University, offered a solution by enlisting a group of Navy Corpsmen as the first class in the newly formed Physician Assistants program. Around the same time in Colorado, Nurse, Loretta C. Ford partnered with physician Dr. Henry Silver to form the first nurse practitioner program at the University of Colorado. Both programs were created to fill in the gap where the physician shortage was threatening the healthcare of the most vulnerable within the American population. Fast forward to today, we still face the problem of physician shortages. APP's have become very important members of the healthcare team. Neurologists are starting to embrace this section of caregivers and figure out ways in which they can enhance a neurology practice.

Nationally most APPs are employed, but their method of practice and responsibilities vary. When trying to determine if a nurse practitioner or physician assistant will enhance your practice, take a look at the financial overview of your practice to see if it is economically viable to add a physician extender. Based on the historical formation and principles of the group, physician assistants' practice and are billed under the physician they work for. On the other hand, nurse practitioners can have their own NPI number and can bill independently. Some choose to partner with a physician in a cost sharing model. There are ways to incorporate physician extenders into an inpatient and outpatient practice. Benefits to the neurologist include increased quality of life, clinic volume, and patient satisfaction. The decision on *if* and *how* to incorporate an APP should be centered around the revenue they create or if the cost sharing model benefits your practice. As more APP's seek neurology training, neurologists have to decide if the commitment to training an APP is beneficial in the long run.

In order to be less reactive and more proactive, it is imperative to understand the environment you are in. Healthcare is changing, and we have to adapt to these changes or influence them by understanding the economic drivers. It is important to learn how to make the diagnosis of myotonic dystrophy with something as easy as a handshake. We also need to understand and train ourselves on the business principles that will allow us to keep our practices financially viable in order to see that myotonic patient. Learning how to run your practice keeps your practice from running you.

Special thanks to Bill Small, David Evans, Stuart Black, Bruce Cohen, Eric Anderson and Tom Holloway for their contribution to this project. For more information on these speakers and the "Business of Neurology" series go to www.texasneurologist.org.

Chaos In Emergence: *A Personal Frightening Experience*

Ernesto H. Guido, MD
Medical Director
Thomas-Spann Clinic
Corpus Christi, TX

The year was 1966 and I was on call as an "Anesthesiologist", in a country where the weapon of choice for dispute was the "MACHETE", and their favorite weekend alcoholic drink was named 'LA CHICHA"***. The combination of the two resulted in fights between friends or families, resulting in horrendous wounds to the face and parts of their bodies. There I am, a second year medical student, with my limited training in Anesthesiology, administering anesthesia for many hours to these poor suffering souls. I recall delivering plaint of Oxygen, the two gases in use were Nitric Oxide and Cyclopropane and to our surprise, most of our patients survived their gruesome wounds and poor anesthesiologists. Lord knows how many prayers in between were made to avoid the worst scenarios. *Fast-forward to the present and I still find myself trying to avoid chaos.*

I have been exposed, as many of us, to the wakening moment after General Anesthesia, and we are usually full of gratifying thoughts about waking up with peace, serenity and not having any memory whatsoever of the difficult journey that our body went through; such a marvel of modern practical science in Medicine, at least that is what we think, until chaos takes place. *The idea that small causes may have large effects, postulated by Edward Loren in his chaos theory, is the core analogy to my chaotic experience. Such an effect of a solitary butterfly, flapping its wings in a far away place.*

During one of my recent hospitalization for a procedure, upon waking up and told that everything was well, and about one hour in the EMERGENCE period, suddenly, without any warning, I became with a sensation of dizziness, feeling like my head was moving from side to side, like I was drunk and then the frightening sensation of my body falling down into an empty space, from which 'I am not going to return", a feeling best described as the "dying process" but still realizing that something is real wrong and that I really need help "right now". I was screaming for help, the recovery room nurse was attending another new case and I do not know how many more and I am very sure she was preoccupied by my behavior but I did not get her hand or re-assurance, her hands were tied, I thought that a wrong medication was given to me and then she managed to show me, somewhat upset, that I was given the Protonix IV.

My wife and son were anxiously waiting to come visit me. The nurse finally came to grab them from the waiting room, she mentioned that I was upset at her but it was only because I was coming out of anesthesia and most likely confused. Upon seeing my son, Luis, I told him with shocking certainty that the nurse was "trying to kill me". You can imagine this caused an alarm in him, large enough to question the nursing staff what was going on and forcefully asking "did you give the right medication?". The staff assured my family, this was a common reaction after anesthesia.

But the sensation continued. The feeling of detachment from my bed lasted a few minutes and was followed by some tingling in my skin, mainly in the course of veins in my arms that I later identified as very subtle fasciculation in my face and extremities.

My Physician came in to my bedside and reassured me that "everything was OK" and that I was going through an anxiety reaction, such behavior or reactions have been extremely incongruous in my life.

When it was time to get out of the recovery room about 5 to 10 minutes later, another wave of similar events took place, with the extremely unpleasant feeling of dying and detachment of my body, this happened for about 3 times. After midnight, the events still came but less and less severe and I was not been able to sleep until the next day.

My metabolic work up was very normal and I was not taking any medication before the procedure that would cause any CNS withdrawal type of reaction.

I was told that my procedure took almost double the expected time and therefore I was under anesthesia for several hours.

After my recovery, my primary physician further inquired about the types of anesthetic agents that I was exposed to, I was maintained mainly on Propofol and the gas Sevoflurane. Upon connecting with the Anesthesiologist, we were told my reaction had nothing to do with the Anesthesia.

EMERGENCE after anesthesia, is defined as the mechanism of waking up, a process that encompasses several arousal brain pathways, responsible for the activation and promotion of Emergence, in which central cerebral regions such as the Thalamus and Hypothalamus and then the Frontal Cortex and others Midbrain regions in between, all playing a critical-complex role..

Complications during Emergence is a well known potential problem, but with limited research in part due to the rather complex actions of anesthetic agents in the Central nervous System and their interactions with multiples receptors and Neuro-transmitters.

The most common complications during Emergence are dependent on multiple factors, including medical comorbidities, type of anesthetic agents and duration of anesthesia. The overall research has been limited and the incidence/frequency reported has been variable, from 3 or up to 20% and studies have been focused more in children (1).

In the most recent reports of Emergence Agitation, comparing Propofol and Sevoflurane (2,3), the agitation was more frequent when Savoflurane was used alone,45% and only 10% in the Propofol Group. I believe the trend in Anesthesia in mild procedures is to use the combination of both, with propofol helping in the development of agitation-delirium.

The anesthetic effects of Propofol in the human brain, has been now extensively studied with PET and fMRI (4). Propofol, sharply reduces the regional glucose metabolism and regional cerebral flow in all brain regions, particularly the hypothalamus; the Thalamocoritcal network is severely suppressed.

The mechanism of action of Propofol increases the GABA mediated inhibitory tone in the CNS, increasing the duration of the GABA-activated opening of the Chloride Channels and resulting in hyperpolarization of the cell membrane. This marvelous drug, also inhibits the N-Methyl-D-Aspartate (NMDA) receptor and has been used to decrease the intracranial pressure. Some reports are indicatives of some neuro-protection and immunomodulation effects in the CNS (5). Propofol has strong similarities in its CNS effect, to Barbiturates, like Thiopental. Side effects during Emergence are mainly related to cardio-vascular and respiratory problems, but cases of psychomotor agitation and anxiety reported.

In regard to the inhaled Gas Anesthetics, the Halo Ethers such as Sevoflurane are one of the most commonly used, in combination with Propofol, and the mechanism of action are upon several ion channels and cells receptors, particularly over the NMDA receptors, GABA and glycine receptors and in doing so, inhibit excitatory ions channels and potentiate inhibitory channels (6) and, again, the interactions with multiples brain pathways and neurotransmitter are rather complex, still more when interacting with others anesthetic agents.

The most frequently studied side effects of Emergence and Sevoflurane, has been the one of Emergence Delirium and agitation, this more extensively study in children's (7); they seem to be at a higher risk for this complication, with incidence ranging between 15 to 20% and less frequent with the use of Halothane and Isoflurane.The effects of this anesthetic has been the subject of multiples studies and

the potential for early or late neurotoxicity and the potential for causing neuro-apoptosis and caspase activation ,as well as Beta-Amyloid (AB) accumulation, has been the subject of studies but without any definite results of causation, though this agent has been in use for well over a century, both their mechanism of action as well as the nature of any neuro-toxic effects remain elusive and studies are fraught with confounders(8).

In retrospective, making a Differential Diagnosis, then, what happens to me?.

I you are an Addiction Physician, you are probably familiar with the "K Hole " trip in people abusing Ketamine and how this is strongly related to the neuromodulator dysfunction that takes place at the NMDA receptor, some of the target of action with Sevoflurane and therefore, not been exposed to Sevoflurane myself in the past, and my prolong exposure, I suspect that one was the culprit and I will be sure to stay away from that chemical, at least for now.

Every day, before my meditations, I always bring to mind the great human emotions and feelings of Love, Empathy, Forgiveness and Gratitude. This last one, a strong feeling of appreciation and a giant thank to my physicians and the multiples personnel who were with me and did help in dealing with my recent chaos. This particular event has also enhanced my feeling of Empathy to those peoples who suffer panic attacks, PTSD and to understand them better and treat them better.

***..CHICHA is an alcoholic beverage made of fermented Pine Apple, with Maize and Panella.The ingredients are variable in different Latin Countries.

References:

1) Marco Casella Et AL, Toward a better understanding of Anesthesia Emergence Mechanism: Research and clinical Applications. World J Methodology. 2018 Oct. 12;8(2),9-16
2) A comparative study of emergence agitation between Sevoflurane and Propofol anesthesia in adults after nasal surgeries. Kim YS et al, Korean J Anesthesiology. 2012 July;63(1):48-53.doi:4097/kjae.2012.63.1.48. Epub.
3) E Card et al, "Emergence from general anesthesia and evolution of Delirium Sings in the Post-anesthetic Care Unit. Br. J. Anesthesia (2014) doi; 10.1093/bja/aeu442.
4) Trends in Anesthesia and Critical Care, Volume 4,issues 2-3,June 2014,pages 76-81.
5) Y Keota et al. "The experimental and chemical pharmacology of Propofol "CNS, Neuroscience and Therapeutic",14(2),96-106,2008 .
6) Soltk et al. Differential modulation of human N-methyl-D spartate receptors by structurally diverse general. Anesth. Analg,2006;102 (5):1407-1411.doi,10.1213/01.
7) Brazilian Journal of Anesthesiology, Volume 64,issue 6,Nov-Dec 2014,pages 413-418..

Neuromonitoring

David B. Rosenfield, MD

While recently driving my daughter to school, she informed me, "Daddy, no one does email anymore." I couldn't help but ponder the obvious: how technology has not only altered knowledge and capabilities of our profession but also how it has influenced our society and culture as we morph from the postal service to email, Twitter, LinkedIn, Snapchat and other domains of social media.

Putting aside memories long ago of party lines in a cottage in Michigan, a quasi-sordid system that nevertheless worked fairly well, one queries how our expanding technology influences everything around us, including the neurology and neuroscience community. These influences intercalate with a myriad of variables, together forming the narrative of our culture.

As our specific community strives to expand neurological knowledge and improve medical well-being, this cultural narrative affects our behavior and goals as we matriculate through administrative systems and bureaucracies, recognize our patients' changing perspectives as well as our own, accept obligations to fill out more forms and leave more voicemail messages on an expanding series of mobile devices. All this reminds us that top-down systems are implemented at their lowest level, be it ordering fast food, interacting with insurance companies or obtaining funding for science.

Who or what influences and processes this tapestry of interactions includes inputs from government and state agencies, private industry and other venues that *de facto* seek to influence who we are and what we do. Throughout this interplay, good or bad, are influences from Hollywood, theater, television series and sports, not to mention sundry others. Further distillation of this perspective highlights that when the average person watches someone else's trade show, such as the Oscars, Grammy or Tony Awards, this means that these organizations, like it or not, are significantly contributing to our civilization's culture. Indeed, one might contend that a partial definition of culture is wanting to watch someone's particular trade show.

Think about it. Would it not be heartening if the average person on the street watched and read about annual neurology and neuroscience meetings, talking about and waiting anxiously for what transpired, waiting to see how presentations were received and who won what award, all coalescing into an excitement about neurological advancement and its impact on the human condition? If so, this yet-to-be popular focus on neurology and neuroscience would promote more research, further advance our diagnostic and therapeutic acumen and, most important, usher an expanding contingent of young minds chomping at the bit to move forward the boundaries of neuroscience and health care.

The trade shows are only a part of this so-called narrative control, which has been an issue throughout civilization, involving politics, religion, economics and just about every aspect of society. We neurological investigators are neither immune nor oblivious to these matters as we interact with them all, seeking greater truths and goals in health care and science.

Several have sought these truths as they wrestled with their own cultural influences. Without going too far back, consider the writings of St. Augustine, one of the most influential people in history, whose "Confessions" argued that Faith was the arbiter of Truth, perhaps unintentionally placing a damper on scientific queries and temporarily instantiating religious organizations as arbiters of things deemed truthful until Copernicus, Galileo, Bacon and others appeared on the planet and promulgated otherwise. Each of these individuals were influenced by their cultural surroundings but maintained their unique, individual focus, catalyzing major change in their current and ensuing generations.

Although some might contend, "There are no truths outside the Gates of Eden," others posit otherwise. Whatever one queries, how we view the world is filtered through our own percepts and influenced by a surrounding cultural discourse that we may not always see but it influences us, making it ever more important to adhere to rigors of science and not be affected by biased systems that intentionally or unintentionally affect our thinking. There is always some type of a nurturing amniotic fluid around us that can provide intellectual and emotional sustenance in our attempt to move the system forward.

Societal norms and appended shibboleths affect us all, whether we identify with members of Emerson's "Self-Reliance" coterie or with the need to fight some external source, as did Ahab against the whale. Thus, whether one investigates neurological modeling, climate change, what to do about immigration or what should be NIH Indirect Costs, we remind ourselves to step back and digest rules of specificity, sensitivity, reliability and validity in anything we discuss or hope to achieve.

Whether we are akin to Emerson or Ahab, fully immersed or inchoate, we interact and connive with and through these surrounding influences. We may not recognize them but they are present and often morph our brains, making us fight demons that are not there or not see demons that are. We think about what we see and hear, and what we see and hear alters our thinking. For this reason, different people process differently the same input, depending upon how much their surroundings have affected their thinking.

For instance, on a simple mundane level, when one turns on an automobile, some might hear only the sound of the engine whereas others relish the thesis that RPMs multiplied against torque equals horsepower and that it is torque, not horsepower that provides the fun of driving. A few might even be warped into pondering whether the sound quasi-replicates complex repetitive discharges on an EMG machine.

Those who cerebrate these perspectives and possibly even

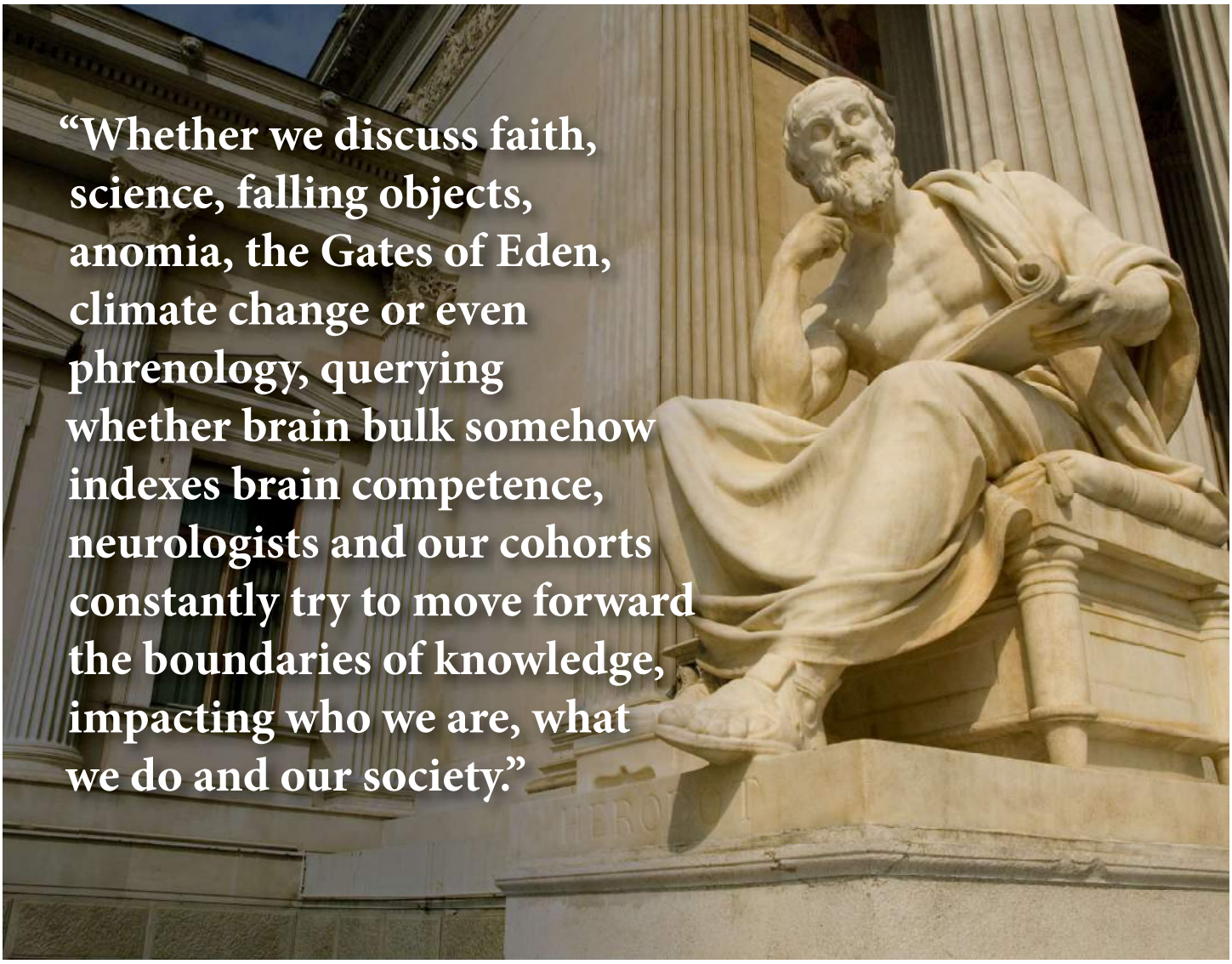
contemplate ephaptic transmission causing CRDs, enter the small cul-de-sac of society's potential changers, looking at the universe through different percepts on a journey to initiate change. These are the ones who move humanity forward, even if they do not pull all the strings. And, they do this through a different perspective of thinking without cognitive prestidigitation or, "Fake News."

The salient issue remains: What is real versus what is known? How we ask these questions is often framed by our observations and external influences, whether Galileo observing the moon or how a heavy versus smaller object falls or St. Augustine pondering how something can have a name in Greek as well as in Latin, yet being neither Greek nor Roman in substance. St. Augustine, rather than pursuing a system of nosology for his not knowing that he described anomia, accepted everything on Faith. The man was brilliant, as was Galileo, whose experiments in thought (and later physically tested) continue to affect our world.

St. Augustine and Galileo, equally intelligent, had a different perspective of events in life, each affected by their individual surrounding milieus and, over time, affecting them in return. And, each initiated changes in how human beings perceive their respective worlds.

Whether we discuss faith, science, falling objects, anomia, the Gates of Eden, climate change or even phrenology, querying whether brain bulk somehow indexes brain competence, neurologists and our cohorts constantly try to move forward the boundaries of knowledge, impacting who we are, what we do and our society.

So, the next time someone turns on their car and thinks about what the engine is doing or the sound it produces, it is good to let their mind travel freely and explore new vistas, even if they have to drive there in a neuromotoring device with a non-neuromuscular transmission. And, none of this should keep them from enjoying the ride or looking forward to our next annual meeting.



Whole Wellness From Within: *Creating and Nurturing Our Own Healer*

Ernesto H. Guido, MD
Medical Director, Thomas-Spann Clinic
Corpus Christi, TX

It is stated by the experts on the healing powers inside us, that such life styles and pathways to better health, has been and are still underestimated. We really do not need to go deep into the philosophical paradigms of Taoism, or to completely follow Al Huang and learn how to move with wind and water, to have a practical grasp and understanding of this antiques self-healing arts but in fact, this can be easy, friendly and enjoyable and cheap and save us a lot of money. And I will say, suffering..

The search for happiness and wellbeing through different means has been an endeavor of many centuries with much practice by the eastern civilizations. We are all, travellers looking for that balance in one or another way, in this extremely complex society but keeping in mind the impossibility of human perfection and the full awareness about the always presence of low hanging diamonds- fruits at a very easy reach.

In his book "The Healer Within",Dr. Roger Jahnke,when talking about the power of selfhealing,he makes emphasis in the close relation-cooperation of our body and mind-spirit. The body is our temple of our life and the mind-spirits the dwellers within that temple and the three together, cooperate to generate the most profound medicine ever known in the history of humanity, lying right within us.

One of the main goals in working to achieve the miracle of healing within us, is to prevent the myriads of degenerative illnesses that plague our society, because, with honesty, as Dr.T Colin Campbell discuss in his book "WHOLE"(Rethinking the Science of Nutrition), we medicate ourselves with toxic concoctions, some of them treat the disease but frequently we have to treat the harmful side effects (1).In his opinion, the name of healthcare system in America is a misnomer and we should call it "A Disease Care System", and I believe he has a very good point..

As a country we are very sick and in spite of billions expended in health care and research, we are not much healthier. Chronic diseases have only increased with time and based on current biomarkers like obesity, diabetes and hypertension, there is further increase in the horizon (2); diabetes itself, according to the CDC reports (3), has more than double from 1980 to 2010.

There are some changes in our life style and behaviors that can help much in prevention.

In my, on the work book, "The three Diamonds of Wellness", ***our first diamond is Our Body,*** fortified by a good program of exercises and linked to our second diamond a holistic nutritional approach and the third diamond, our Mind-Spirit..

There is plenty of research about the benefits of physical exercises and our cardiovascular and neurological systems but we have to caution that excessive exercise is not more beneficial and overdoing can bring serious consequences.

The American college of Sport Medicine and Kiser Permanente, in April 2015,discussed and developed the Physical Activity Vital Sign (PAVS). This became a call to action for the Medical Community to always implement the PAVS in daily practice with every patient. .

The wellness coming from your exercise is multi-factorial, including changes in Neuro-transmitters Dopamine, Endorphins an serotonin as well as increase in Brain derived Neurotropic Factor, facilitating NEUROPLASTICITY (4). Recent research (5), indicating anatomical changes after exercises over the Hippocampus volume and increase connection with the prefrontal cortex. Most recent research even indicate a reduction in Dementia (7), and certain cancers. Reports in the association of aerobic exercises with greater connectivity of the cerebral default mode network as well as allocations of brain resources and therefore, physical activities promote brain maintenance and cognitive reserve (8).

Now days, one of the first prescriptions that is coming from a Neurologist, in cases of Mild Cognitive Impairment is "Taking Your Brain to the Gym".

Important questions still remain about this subject.

One of the great tools available nowadays, in enhancing our link between our body-exercises and mind, is the program that I have outlined in my article on May 2019,about Medical Qigong..

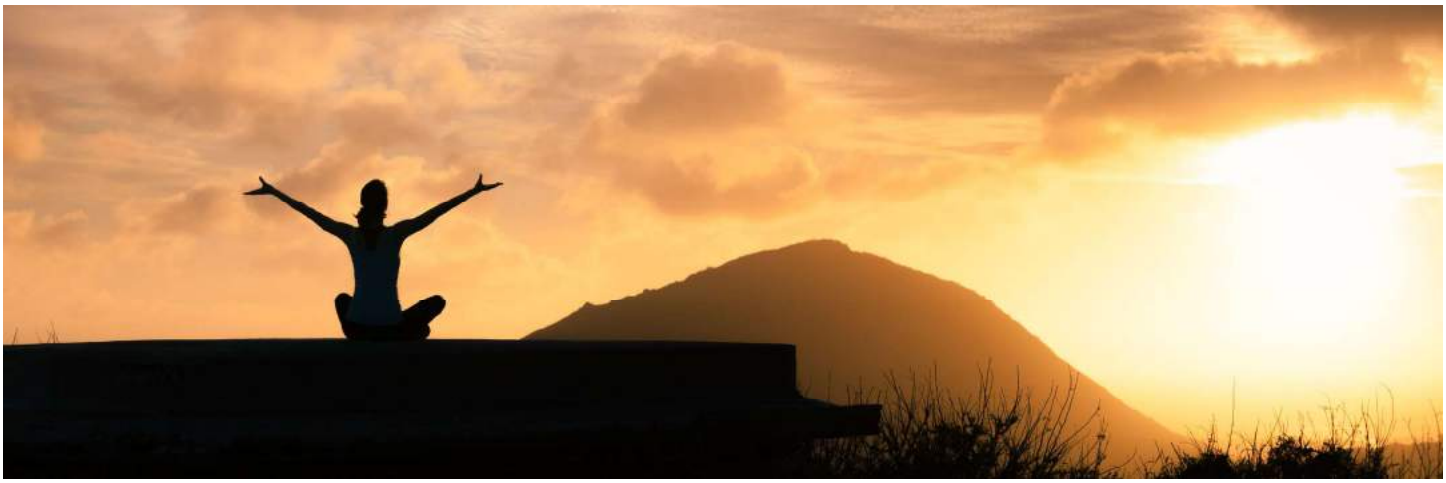
My second diamond of wellness is NUTRITION and lets start with the quote of HG Wells "History is a race between education and catastrophe".

There is not a topic so critically important as well as controversial and full of misinformation as is nutrition. So contaminated by the Reductionist Approach at all its level and the great self-interest forces behind. Nutrition is a tremendous tool in helping us in finding the healing power in ourselves and what we eat everyday, can give us a healing potential more effective and faster than the most expensive drugs, with rather extensive Bibliography, most recent article at our NEUROLOGY journal, AAN (8), Dietary patterns in early life pay dividends for midlife cognitive performance..

I have explored these issues for the last few years and obtained a Master Certificate in Nutrition with the AFPA;I was dismayed of the lack of knowledge and misinformation in our health system and society in general.

Our recommended Basic Food Pyramid, sponsored by our government and major health organizations, give us as dietary guidelines a healthy diet to have 45 to 65% of carbohydrates, 20 t0 30% of fat and 10 to 35% of proteins, however according to extensive research, our western society is eating so much proteins of animal source, this related to causing some cancers. The WHO finally, in 2015,declared meat as cancerogenic, particularly the one processed, which are the majority. The barbeque meats are a different enemy. There is great and solid discussion about the real benefits of "cow milk", issues strongly protected by the big foods corporations.. The source of the carbohydrates is still miss-informed.

With few exceptions, according to much solid research, the best food intake lifestyle considered the ideal human diet is: "Consume



plant based foods in form as close to their natural state as possible, the so call Holistic approach; eat a variety of vegetables, fruits, raw nuts, seeds, legumes and whole grains. Avoid at all costs processed foods and animal products. Stay away from added salt, oil and sugar. Aim to get 80% of your calories from healthy carbohydrates, 10% fat and 10% from proteins and once you train your buds-taste, you will be surprised how delicious treats you will find. This is been called The Food Plant Based Diet (WFPB) or WFPB life style. Reading "Whole " by Dr. T Colin Campbell, extremely instructional.

We are aware of the beneficial morphologic changes in the brain, particularly with the Mediterranean Diet. Needle to say, the help to our environment, following the above-described life style, is enormous.

The third and last diamond of wellness is mind and soul connections, this section is perhaps the oldest techniques used by human kind for healing but with significant reliance in beliefs and faith and at times been associated with deceptions and abuse.

The Eastern cultures have been pioneer on techniques enhancing the Mind-body interactions.

As I mentioned earlier, one of the best complete practices that I have experienced in making this connections, is the one pioneered by Dr.Jahnke, using traditional Chinese techniques, to release our self internal healer, using ancient practices of gentle movements of the body (Qigong-Taichi), self applied massage, breathing practices and deep relaxation and meditation. Being the breathing a common phase in all this activities, and a powerful tool to enhance our parasympathetic Chain; I believe this part of all our mind-body exercises, is the most powerful healing activity..

Our brain contain roughly 1,1 trillion of cells and several trillions of synapses, over the course of one minute, quadrillions of synaptic events occur, so our brain is in constant changes, making lasting changes and the core of the science of NEUROPLASTICITY. We for sure know that the power to implement those changes lies within us, our internal Sage, our god. .

In regards to the meditations, there is not one technique better than other; most of them follow the basic principles of live the moment, breathing techniques and relaxation. I have taken a personal course in Transcendental Mediation (TM) and several courses in Mindfulness Mediation but I am far from been an expert in the cognitive and neural mechanisms interacting in meditation and as anything else, done improperly and excessively, yes, can have side effects in some reports, as high as 25%, most of them are transient but the positive outcomes such as well being and positive emotions are the most common responses (10).

There is a solid amount of information in the anatomical changes following meditation, particularly at the level of the Hippocampus, Prefrontal Cortex and decreasing the volume of the Amygdala.

TM is based on the teaching of Maharishi Yogi, expressing his teaching in spiritual and religious term; is a form of silent Mantra Meditation, I did not like it much, otherwise I can not make any further comments.

I became more familiar with Transcendental Meditation, taking several courses, this technique I found more diverse, and with strong use of breathing techniques, based on scanning your body and live the moment and present, to reinforce centers of kindness and compassion. We can apply and practice mindfulness in all activates of our life, such as eating, walking, driving etc. In my personal practice, I have added some portions of Qigong meditation. If anything is extremely helpful, is the breathing-awareness technique and began…"close your eyes and found your comfortable zone and think about LOVE, feel the real love, EMPATHY, FORGIVNESS and then GRATITUDE…."then challenge your breathing, extend your exhalation giving a massage to your belly-micro biome and have a relaxing and pleasant holydays, be the good forces of self-healing accompany you always.

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Bibliography;

1)..B Starfield "Is US health really the best in the world?'JAMA 284,No 4 (2000),483-88.
2) Nancy hellmich "US Obesity Rate Labeling Off at about one third of adults" USA Today, January 30,2010..
3) US Centers for Disease Control and prevention "Crude and Age-adjusted Percentage of Civilians, on-institutionalized population with diagnosed diabetes, united States 1980-2010,last modified 4/26,2012.
4) Book, Neuroplasticity (your brain superpower),By Philippe Douyon MD,April 23th,2019.
5) C, W Cotman et al. Exerc Sport.Sci Rev, 2002,30 (2),75-9.-
6) Voss M W et al. Plasticity of brain network in a randomized intervention trial of exercise training in older adults. Front Aging Neuroscience, 2010; 2:32..
7) Alzheimer Brain biomarkers changes in middle age adults. Bert V et al, Neurology 2018,and April 13.PIT: 10.1212/WNL.
8) Neurology, Volume 92,Number 14,page 654,April 2,2019.
9) Dahl et al "Reconstructing and deconstructing the self: cognitive mechanism in meditation practice. Trends Cogn Sci. 2015.September; 19(9): 515-23.doi.