TEXAS NEUROLOGICAL SOCIETY WINTER 2021

Broca's Area

The Voice of Texas Neurology

President's Message

Waleed El-Feky, MD

Although the TNS meeting was canceled last summer, the TNS committees and administration have been busy addressing the new challenges imposed on all of us by the Covid19 pandemic and continuing the various activities of the TNS.

The education committee had several meetings to work on our upcoming winter meeting. They put together an exciting group of speakers covering a wide spectrum of topics and updates for all neurologists. This meeting will be the first ever virtual educational meeting for the TNS. We are excited and looking forward to a very successful program in February.

The medical economics committee continues to work diligently to update the members with changes in the business of neurology. Last summer, they presented a highly informative video series on telemedicine implementation, and coding. Together with the legislative committee, they presented an update on the governor's directive to continue parity reimbursement under the emergency rule. You can find these excellent videos at the TNS website. In December, the committee organized a webinar to explain the recent coding changes and its impact on neurologists. It was a valuable update.

The advocacy committee has been busy following the TMA and AAN initiatives as they pertain to the TNS membership. Given the TNS size and stature as the largest Neurological society in the nation and one of the largest specialty societies in Texas, the TNS is frequently asked to support state and national advocacy efforts. Examples of such initiatives include the support of the 2021 Centers for Medicare and Medicaid Services Medicare Physician Fee Schedule, as well as well as a one-year waiver of budget neutrality requirements to avoid payment reductions which have been a concern during the COVID-19 public health emergency. The committee chair presented neurology related issues at the TMA Advocacy Retreat in December and has been working with the TNS lobbyist to prepare for the 2021 legislative session.

TNS is now on social media! One of the new and exciting changes to TNS is our increased activity on social media. The TNS Facebook page continues to grow as well as our followers on Twitter. Please make sure you like us on Facebook and follow us on twitter @Texas_Neuros where you will find useful information and stay up to date on TNS activities.

The residents committee put together a curriculum on the business of neurology for residents. The curriculum has been accepted by residency programs around the state. Eight residents have signed up so far to participate in this rotation where they will learn the business aspects of a neurology practice.

Several high-quality researchers from around the state applied for the TNS 2021 grant. Those applicates were, then, reviewed by the grants committee. This is perhaps the youngest committee at the TNS. Though it is only two years old, it has, so far, supported excellent research projects around the state. This year's grant was awarded to support a very exciting project on dance therapy for patients with Parkinson's disease. We look forward to the results of the exciting research projects the TNS is supporting at future meetings.

Despite the challenges of 2020, the TNS continues to work on multiple fronts to benefit its members. The TNS gets its strength from its large number of members, excellent educational programs, advocacy work, resident involvement, and the dedicated group of interested neurologists who form the TNS board and committees.

I am thankful for our highly supportive members, and for our dedicated and highly motivated board and committee members, as well as our superb administrative team. With such a combination, I am confident TNS will continue to get stronger and more beneficial for our members and patients.

CONTENTS

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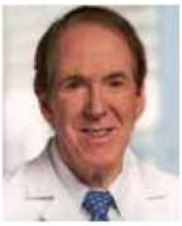


Editor's Notes

Randolph W. Evans, MD

Unfortunately, the 21st Winter Conference on February 6 will be virtual with on-demand presentations available January 27. But the program will be GREAT! Padraig O'Suilleabhain, adult program director, Gary Clark, pediatric program director, and the education committee have planned an excellent program.

WHAT IS THE CAUSE AND TREATMENT FOR HEADACHES? ANSWERS FROM MESOPOTAMIA AND ANCIENT EGYPT

We are still struggling to find the cause and treatments for headaches. Hypotheses about the role of CGRP in the mid 1980s by Lars Edvinsson have result in the small and large molecule CGRP antagonists. People have always speculated about the cause of headaches and tried any number of treatments. Just think about treatments without evidence your patients have tried.

MESOPOTAMIA. In 7th century BC, in the Assyrian royal capital of Nineveh (located in current day Mosul), the first universal library was created. In the cuneiform tablets in the Ashurbanipal library, you could find the tale of Gilgamesh, rituals, prayers, omens, royal letters, healing texts, rituals and incantation, and magical and medical prescriptions (Panayotov SV. How to cure a 'headache' in a Mesopotamian way? Hypotheses. Available at https://recipes.hypotheses.org/880; Fales FM. Chapter 2: Mesopotamia. Handb Clin Neurol. 2010;95:15-27.

On behalf of King Assurbanipal (king of the world, king of the land Assyria, to whom (the gods) Nabû and Tašmētu granted understanding), an encyclopedic medical handbook was produced with medical prescriptions, incantations, and rituals with chapters or tablets ordered from head to toe (Babylonian Medicine Handbook) as a reference for the royal palace.

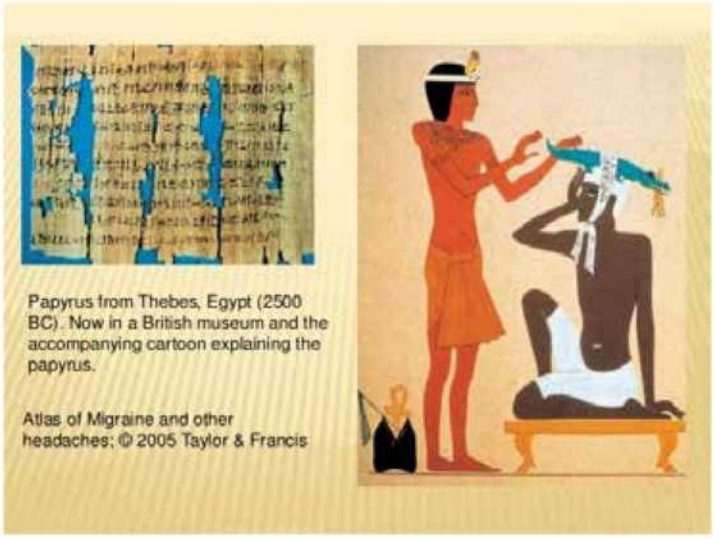
According to the third tablet, headache or "seized forehead/temple/brow" was caused by a ghost. If the headache was not helped by bandages or an incantation, proceed as follows:

"You slaughter a captured goose. You take its blood, its throat, its gullet, its fat, the rind of its gizzard. You char (them) over charcoal. You mix (them) within cedar 'blood', and then three times recite the incantation 'Evil Finger of Mankind'. You repeatedly anoint his head, his hands and everything that affects him and he shall get better. The 'headache' will be eradicated (Scurlock, J. 2006. Magico-Medical Means of Treating Ghost-Induced Illnesses in Ancient Mesopotamia. Ancient Magic and Divination III. Leiden–Boston:."

So next time you're stuck, send this prescription to your favorite specialty pharmacy and give it a go. Tell your patient it was the preferred treatment recommended by the doctors for the king of the world.

ANCIENT EGYPT. It is estimated that less than 0.01% of Egyptian medical papyri are available with most material on headache in the so-called magical texts of the New Kingdom around 1550 BC (Karenberg A, Leitz C. Headache in magical and medical papyri of ancient Egypt. Cephalalgia. 2001 Nov;21(9):911-6). According

Figure. K2566 from the British Museum



to the Papyrus Ebers, "Magic is effective with medication, and medication is effective with magic." If you don't believe in magic or medications without efficacy, believe in the placebo effect.

The four parts of the head reported as affected by headache were the top and back of the head, temple, cheek bone, and nape as well as the head or skull as a whole. Little detail is available about clinical features of headaches. Headache was caused by peculiar pain-matter demons.

The papyrus Ebers listed various remedies including animals drugs (e.g. catfish skull, perch bones, stag's horn, goose fat), vegetable drugs (e.g. honey, reed, frankincense, lotus), and mineral drugs (e.g. natron, malachite, and stibium) applied to the head. There were a variety of magical incantations invoking falcon-head Horus, the son of Isis and Osiris; Ibis-head Thoth, the divine patron of all magicians and savants; and the sun-deity, Ra. Ra was stated to have suffered headaches.

Clay crocodile figures with herbs in the mouth may have been placed on the head to transfer the pain (Popko, L. Some Notes on Papyrus Ebers, Ancient Egyptian Treatments of Migraine, and a Crocodile on the Patient's Head. Bulletin of the History of Medicine 2018; 92(2), 352-366)

← BACK TO PAGE 1
NEXT PAGE →

The Business of Neurology Video Series

A four-part video series hosted by Eddie L. Patton Jr., MD, that includes: **Contract Negotiations, Update on Coding for Neurologists, Practice Enhancement Through Increased Service Lines** and **Using APP's in Neurology Practices**.

Go the TNS website and log in. All videos are found under the *members only* tab.

Find TNS On Social Media!

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

@TexasNeuros @Texas_Neuros

Business of Neurology Resident Rotation is Open!

The Texas Neurological Society resident committee has developed and is currently accepting applications for a "bonus" rotation for senior neurology residents. This five-to-ten-day rotation places a resident in a practice where they will learn about Medicare and Medicaid plans, laws and benefits, coding rules, billing, and payment processes for patients and more as they relate to running a practice. It is a "behind-the-scenes" look at the business of neurology meant to close the knowledge gap for residents intending to enter clinical practice. The rotation started in November 2020 and will be ongoing indefinitely. Several TNS members around the state have opened their practices as rotation locations, for which we give them our greatest thanks. If you are a resident or know of a resident that would like to participate in the program, please go the TNS website (www.texasneurologist.org) and click on the information found on the home page.

← BACK TO PAGE 1
NEXT PAGE →

In Memory of Anand Mehendale, MD

Dr. Anand Wasudeo Mehendale, 67, a neurologist and addiction medicine specialist who made it his life's mission to care for the ailing and to promote recovery in those battling addiction, died December 19th, 2020 of complications arising from CoVID-19.

Born in Barsi, Maharashtra, India on April 13, 1953, Dr. Mehendale earned his medical degree from B.J. Medical College, graduating in the top of his class. After arriving in the U.S. in 1977, he went on to complete his neurology residency at the University of Arizona before completing his fellowship in higher cortical dysfunction, epilepsy, neuropsychiatry and EEG at the UT Health Sciences Center in San Antonio. After a stint working as Chief of the Neurosciences Division and Director of Medical Services at the Kerrville State Hospital and serving as Medical Director of La Hacienda Treatment Center, Dr. Mehendale went into private practice, forming Phoenix Medical Associates in 1998, where he worked dutifully until his passing.

During his time serving the Kerrville community, Dr. Mehendale built a reputation for intelligence and generosity, treating patients who others were unable to diagnose and personally ensuring that no patient was denied treatment because they did not have the means to afford it. As a result of his efforts and skill, Dr. Mehendale earned the distinction of Hall of Fame Legacy Member of the Texas Super Doctors list compiled by Texas Monthly, an accolade given to those identified as a Super Doctor by their peers for at least 10 years.

A doctor in recovery himself, Dr. Mehendale was a pioneer and visionary regarding physician health issues. He was instrumental in the development of the Texas Medical Board's Texas Physician Health Program, serving as the Presiding Officer of the Governing Board, which advocated for protecting the health of medical professionals affected by substance use disorders, physical illness and impairment, and/or psychiatric conditions through the use of monitored recovery programs adapted to their specific needs.

Those who knew Dr. Mehendale will remember him for his goofy, offbeat sense of humor and thoughtful disposition. A true dog lover, he always enjoyed coming home to spend time with his pets. In his free time, he enjoyed playing table tennis, driving cars, reading books on and exploring spirituality and philosophy, and watching sports as a diehard Spurs and Cowboys fan. In the end though, nothing brought him more joy than spending quality time with his family, whether it was on vacation to an exotic location or a quiet night gathered in the living room sharing stories and laughs.

Dr. Mehendale is survived by his wife of 42 years Sophia Mehendale and their three children, Rachel and son-in-law Matt of Georgetown, Ryan of

Austin, Nick of Chicago, his two older brothers Avinash and sister-in-law Pushpa and Anil and sister-in-law Jayashree, both of Pune, India, in addition to many nieces and nephews who adored him. In lieu of flowers or gifts, the family requests those who wish to honor Dr. Mehendale make donations to Freeman-Fritts Vet Clinic & Shelter and Turner Recovery House. Details on his memorial service forthcoming.

Houston Neurologist Elected to TMA Board of Trustees

Kimberly Monday, MD was elected to the Texas Medical Association (TMA) Board of Trustees. TMA's House of Delegates policy-making body ratified Dr. Monday's election during a virtual meeting [on Sept. 12] to certify the last of this year's TMA elections.

An active member of TMA since 1997, Dr. Monday serves on the TMA Council on Legislation and the Prior Authorization Task Force. She served on the TMA Council on Socioeconomics and as a delegate to the TMA House of Delegates in 2004-05 and 2010-20. She also served on TMA's Committee on Continuing Medical Education and TEXPAC, TMA's political action committee.

Dr. Monday, who has practiced for 23 years, is an associate professor in the Department of Neurology at McGovern Medical School at The University of Texas Health Science Center at Houston, and serves as the vice chair of clinical operations for the Department of Neurology. She is the co-founder of the Houston Neurological Institute.

Dr. Monday is a member and former president of the Harris County Medical Society where she also served on the Board of Medical Legislation and the executive board. Her leadership also extends to the community at large; Dr. Monday serves as chair of the Harris Health Care System Board of Trustees, and on the Memorial Hermann Physician Network Board of Directors.

Excerpt from Texas Medical Association news release, Sept. 12, 2020

Eddie Patton, MD elected as alternate delegate to the AMA

Thirty-nine Houston-area physicians have begun terms of service in Texas Medical Association (TMA) leadership positions, while caring for patients and managing medicine's response to the COVID-19 pandemic. Eddie L. Patton Jr., MD, a neurologist in practice for nine years, was elected alternate delegate to the Texas Delegation to the AMA House of Delegates.

← BACK TO PAGE 1

NEXT PAGE →

Texas Neurological Society Update

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

With millions of dollars spent by candidates from both major political parties and statewide voter turnout exceeding 11 million for the first time in history, the 2020 election saw unprecedented levels of political spending and voter engagement here in Texas.

Boosted by a closer-than-expected 2018 U.S. Senate race between Republican Ted Cruz and Democrat Beto O'Rourke, and with polls showing President Donald Trump struggling to maintain support among key constituencies including women and suburban voters, Texas Democrats had high hopes of carrying the statewide vote for the first time in more than two decades and winning a host of competitive congressional and legislative seats downballot.

Ultimately, hopes for a Democratic political takeover largely fizzled as Republicans seemed to hold serve against the strongest and most well-funded political challenge in decades. President Trump carried Texas somewhat comfortably, as did U.S. Senator John Cornyn and the rest of the statewide Republican ticket. It was also a good night for incumbents in the Texas House of Representatives, where all but one Republican and one Democrat managed to retain their seats, effectively maintaining the 83-67 split between the Republican majority and the Democrat minority.

Though the Texas Senate had fewer competitive elections this cycle, we nonetheless saw a slight shift of power in the state's upper chamber as Republican Pete Flores lost his bid for reelection to Democrat Roland Gutierrez. Gutierrez's election may prove pivotal in the upcoming session, since it effectively denies Lt. Governor Dan Patrick and the Republican Senate the 3/5 supermajority needed to consider legislation in the Texas Senate, thereby giving Senate Democrats the power to block legislation for the first time since 2013.

NEW LEADERSHIP

As we approach the 87th Texas Legislature in January, the House of Representatives will welcome its third Speaker in the past three sessions. House State Affairs Chairman Dade Phelan (R-Beaumont) announced shortly after Election Day that he had secured the support of a majority of his colleagues to capture the Speaker's gavel and lead the Texas House through the 2021 session.

Speaker Phelan will face a legislative session beset by historic challenges: the COVID-19 pandemic, the politically-fraught process of redrawing state and federal legislative boundaries, and a projected budget deficit of $4.6 billion to reconcile. As Speaker, Phelan will also have the opportunity to name his own leadership team to chair the various committees of the Texas House, including the House Committees on Public Health, Insurance, and Human Services. The TNS Leg-

← BACK TO PAGE 1
NEXT PAGE →

islative Affairs team will continue to work with Speaker Phelan and his new leadership team to ensure that neurologists remain well-represented and well-positioned for a successful legislative session.

TELEMEDICINE

The challenges of COVID-19 have impacted nearly every aspect of our society, including the way physicians interact with patients. Because of COVID 19, there has been a dramatic increase in the use of telemedicine solutions that allow physicians to treat and diagnose their patients remotely.

While telemedicine services have existed in some form for many years, they've only recently received the legislative and regulatory guidance to be widely adopted in the state of Texas. In 2017, Senator Charles Schwertner, MD (R-Georgetown), and Representative Four Price (R-Amarillo), passed SB 1107 — a groundbreaking bill that allowed the use of telemedicine to establish a valid physician-patient relationship and created the first regulatory framework for the provision of telemedicine in Texas.

Notably unaddressed in that bill was the issue of pay parity for physicians; ensuring that doctors are appropriately reimbursed by health plans for services provided through telemedicine. In the early days of the pandemic, Gov. Greg Abbott sought to address this issue through executive order by requiring all state-regulated health plans (Texas Medicaid, ERS, TRS, individual health plans sold on the state exchange, etc.) to compensate physicians at the same rate regardless of whether their services were provided in-person or remotely through an appropriate telemedical service.

The upcoming session will see a concerted, bipartisan effort to make the Governor's temporary order permanent. Representative Tom Oliverson, MD (R-Tomball) and Representative Julie Johnson (D-Dallas) have filed HB 515 and HB 522, respectively, to settle the issue once and for all and ensure that physicians and other providers are appropriately compensated for services provided through telemedicine. The TNS Legislative Affairs team will be actively monitoring both bills this session as we work to protect the practice viability of our members utilizing telemedicine to treat their patients.

MEDICAL CANNABIS

As of December 1, a number of legislative proposals have already been pre-filed in the Texas House and Senate which touch on the issue of marijuana regulation in one form or another. These proposals range from modest adjustments to the state's existing Compassionate Use Act, all the way to full legalization and taxation of recreational marijuana.

To help guide the efforts of the Texas Neurological Society on the issue, the TNS Board of Directors conducted a member survey to determine attitudes about medical cannabis and what position, if any, TNS should adopt with regard to this rapidly-changing public policy landscape.

The survey results showed 72.9 percent of neurologist respondents were supportive of the state's existing Compassionate Use Program for medical cannabis, while 57.2 percent indicated support for a less restrictive program that would allow physicians to prescribe cannabis to patients without regard for an arbitrary, legislatively-approved list of medical conditions. Further, 54.3 percent of respondents expressed support for allowing physicians to prescribe cannabis with both low and high ratios of CBD to THC for the treatment of chronic pain and other medical conditions. Based on this feedback, the Texas Neurological Society put forth the following position statement on medical cannabis laws in Texas:

The Texas Neurological Society supports a medical cannabis policy for the state of Texas that would allow a physician with a relevant medical specialty to prescribe medical cannabis containing variable dosages of tetrahydrocannabinol (THC) and cannabidiol (CBD) for the treatment of any medical condition they feel is appropriate.

Senator Jose Menendez (D-San Antonio) has already filed SB 90, which would create the legal and regulatory framework for a substantially expanded medical cannabis policy in Texas. The legislation would permit the licensure of medical cannabis dispensaries in Texas and adopt a more permissive policy with regard to physician prescribing. The issue is a deeply personal one for Senator Menendez, whose wife has multiple sclerosis.

In the Texas House, Representative Lyle Larson (R-San Antonio) has already filed HJR 28, a proposed amendment to the Texas Constitution that would authorize the regulated cultivation, sale, and possession of cannabis for medical use. If passed by the legislature, the amendment would be put to a statewide vote to ratify the change to the constitution. Representative Alex Dominguez (D-Brownsville) has also filed HB 43, which would, among other things, expand the definition of a medically eligible condition to include any medical condition for which a physician determines that medical cannabis is a medically necessary treatment.

The TNS legislative affairs team will continue to monitor all legislation related to medical cannabis as we work to craft a medical cannabis policy that supports the independent medical judgment of physicians to determine whether such treatments would be appropriate for their patients.

This is typically the time when we ask you to please save one 'first Tuesday' of the month to attend the TMA's 'First Tuesday' - your chance to lobby at the Capitol. Yes, we are still saying that. I'm sure that the legislative session will look completely different than what we've seen in the past, but legislators are still intent on making laws here in Texas, many of them will affect healthcare, and neurologists need to be available to articulate our opinion about laws that affect us and our patients. Please contact us thru our executive director, Ky Camero, if you would like to help advocate for the house of medicine here in Texas.

← BACK TO PAGE 1 NEXT PAGE →

Outlook on Health Care Reform and the AAN's Position

James C. Stevens, MD, FAAN, President, AAN

After a whirlwind election season, it appears at this writing in mid-November that Joe Biden is president elect and will take office on January 20, 2021. Democrats maintained their majority (albeit reduced) in the House of Representatives, and control of the Senate will not be finalized until after the two runoff senatorial elections in Georgia in January.

What is 100-percent certain is our leaders must again take on health care reform in the coming months.

Any attempts to change health care policy will be informed by the hardships visited upon Americans due to the COVID-19 pandemic. Millions of people were laid off temporarily or permanently and their employer-sponsored health care benefits were terminated. Sudden loss of income made it difficult to impossible for people to pay for COBRA coverage, see their doctors, or continue their prescriptions. People also missed out on physician care because their doctors were closed during shutdowns or patients were afraid to risk coronavirus infection by going to their appointments.

Telehealth—a service the AAN has been advocating for the past few years, particularly with regard to compensation and nationwide acceptance by payors—came to the rescue for many providers and patients, and it could be an area where the Trump and Biden administrations find common ground. But telehealth is just a tool, not a policy.

The AAN took a neutral stance during the formation and deliberations over Obamacare. However, as the Trump administration announced it was going to create its own health reform alternative, the leaders of the Academy created a set of principles that were neither Republican nor Democrat, but focused on the care of our patients and support for our profession as neurologists. And so, before the battle is joined on Capitol Hill, I wish to reiterate the AAN's Principles for Health Care Delivery:

- Access to high-quality health care and preventative care through insurance coverage for all, including those most vulnerable to health care disparities, regardless of pre-existing conditions
- Appropriately value cognitive care services
- Limit administrative requirements and advocate for EHR functionality to ensure that physicians spend as little time as possible on low-value clerical work, and as much time as possible engaged in direct patient care
- Continue efforts to streamline EHR interoperability and reduce data blocking to allow any willing provider to participate in a qualified clinical data registry

- Improved valuation of patient-centered care setting alternatives including telemedicine and other innovative care models
- Improve efforts to reduce spending on pharmaceuticals and other key drivers of health care expense through cost transparency and permit the negotiation of drug costs by Medicare
- Medical liability reforms to reduce the cost of premiums and defensive medicine
- Preservation of the physician-patient relationship including independent medical decision-making and patient access to needed treatments and education
- Protect access to neurology care in all settings, including small and solo practices
- Achieving these goals won't be easy. Entrenched positions will need to be bridged. Special interests will need to compromise. But we cannot continue to have the world's most expensive health care without being the world leader in healthy outcomes and financial value.

Rest assured, we will continue to fight for the principles above and we will keep you updated on our progress along the way through AANnews and Capitol Hill Report on AAN.com and in your inbox. You can get engaged on issues by using #AANAdvocacy and responding to our advocacy email alerts where you can raise your voice to help sway Congress to do the right thing for the health and welfare of all Americans.

← BACK TO PAGE 1
NEXT PAGE →

Multiple Sclerosis & The National MS Society: A physician turned patient's perspective

Lisa Doggett, MD, MPH, FAAFP

I woke up dizzy on a Monday morning in November, 11 years ago. I didn't think much of it, and I went to work, as usual, at my small community clinic in Central Austin. As the week wore on, my symptoms persisted, and I began to worry. When I started to have mild diplopia, I needed to seek care.

I sought advice from a neurologist acquaintance who did me a favor by fitting me in for a quick exam over her lunch hour. The exam was normal. She told me I was probably OK.

But my dizziness continued, and I started to have another weird symptom: taste changes. I couldn't understand what was going on, but I knew I wasn't OK.

A few days after that initial consultation with neurology, I made an appointment with an ENT doctor. He listened to my story and asked lots of questions. My hearing tests were normal and so was my exam, except for subtle nystagmus. Nevertheless, he ordered an MRI, revealing my diagnosis: multiple sclerosis.

I was lucky. Most people with MS wait months or even years before they are properly diagnosed. My diagnosis took eight days because, as a physician, I understood something was wrong despite a normal exam. I knew the ENT doctor who fit me into his busy schedule, and I had the support and resources to get help fast and start treatment immediately. I worry when I think of others who can't access the care they need. But as physicians, we can help.

First recognized as a distinct disease in 1868 by French neurologist Jean-Martin Charcot, multiple sclerosis is a chronic, autoimmune condition that damages myelin and disrupts communication between the central nervous system and the rest of the body. Despite much research and many theories, the cause remains unknown. Common symptoms include visual changes, fatigue, numbness, weakness, cognitive changes, bladder dysfunction, depression, and impaired mobility and coordination. Optic neuritis is the presenting syndrome in 20 percent of patients with MS. While it can occur at any age, most people with MS are diagnosed between ages 20 and 50. More women are affected, with a female to male ratio of about three to one. The presentation and symptoms, as well as the natural course of the disease, can differ considerably from person to person.

I'm embarrassed to admit, as a family doctor, MS never occurred to me as a diagnostic possibility in my own case. My husband, an internist/pediatrician didn't suspect it either. Neither of us had seen more than a handful of MS patients in our years of practice, and we had never diagnosed anyone with MS.

Yet nearly a million people are living with multiple sclerosis in the United States. MS should have been on our radar. Because its presentation is so variable, and because most people with MS have the relapsing, remitting type and will get better between exacerbations, the diagnosis can be tricky. As neurologists, you should keep MS in mind as a potential cause when you see someone with unusual neurologic symptoms. Ask about past episodes that may indicate a suspicious pattern. Consider an MRI, even for those with a normal exam, if you think MS is a possibility.

As recently as three decades ago, MS was often a devastating diagnosis, leading to long-term disability with no good treatment options. Now, nearly two dozen disease modifying medications are FDA-approved to reduce the progression of MS and limit disability. Diagnosing MS and starting treatment immediately can significantly improve a patient's prognosis and quality of life.

The National MS Society (NMSS) had been a critical driver behind MS research, advocating for support at the national and state levels and directly funding research studies. It also is an important resource for patients, their caregivers, and their physicians. In addition to providing solid, evidence-based educational information on their website, the NMSS can connect patients with MS specialists around the country.

The MS Navigator Program (https://www.nationalmssociety.org/Resources-Support/Find-Support/Ask-an-MS-Navigator) provides direct one-on-one support for people affected by MS including:

- Information and education
- Emotional support
- Connecting with others with MS
- Navigating the complexities of the health care system: finding a neurologist, accessing benefits and medications, etc.
- Resources to address financial issues and plan for the future
- Wellness strategies
- Assessment for case management

There is no charge to participate, and the discussions and information shared are confidential.

Another helpful resource for neurologists is Project ECHO (https://www.nationalmssociety.org/For-Professionals/Clinical-Care/Professional-Education/ECHO-MS), a guided practice model that increases workforce capacity of neurologists and other clinicians to provide best-practice specialty care for MS patients and reduce health disparities. The field of MS research is changing fast and keeping up can be a challenge. Project ECHO participants join an interactive video conference facilitated by one of three hub sites and are supported by MS experts in their care of patients with MS.

For me, in addition to reliable information, the NMSS has offered a community of fellow "MS Warriors" and supporters. It has empowered me to share my story, lobby at the State Capitol on behalf of the MS community, and join nearly ten thousand fellow cyclists to ride the MS 150, a 150+ mile bike ride from Houston to Austin (twice!).

Despite three relapses, I remain almost symptom-free with no discernable disability today, thanks to high-quality medical care from an excellent neurologist, who specializes in MS, and effective treatment options. I work full-time, exercise every day, and remain active in my community and with my family.

I encourage all my fellow physicians to become familiar with the resources offered by the NMSS and to seek to improve identification and treatment of all people living with MS.

← BACK TO PAGE 1

NEXT PAGE →

The Revised 2021 Medicare Physician Fee Schedule (MPFS)

Stuart B. Black, MD, FAAN,
AAN Medical Economic and Practice Committee

IMPORTANT 2021 LARGE-SCALE CODING CHANGES FOR E/M OFFICE OUTPATIENT CODES AFFECTS OUTPATIENT CPT CODES 99201 – 99215

1. History and Physical Examination:
   H&P eliminated /no longer required as an element for code selection
   Requires H&P documentation only as *Medically Appropriate* for visit
2. Documentation and Reimbursement for services rendered:
   Entirely based upon Medical Decision Making (MDM) *or* Time
   Choose *either* MDM *or* Time to document the E&M level of the visit
   E&M code selection criteria now *driven by* MDM and Time
3. New Patient Code 99201 has been eliminated
4. The five levels of coding for Established Patients has been retained
5. Revision of the code definitions
6. Revision of the Times and MDM process for all codes
7. Adjusted wRVU values:
   An overall increase in wRVU for E&M visit codes
8. Reduction of RVU Conversion Factor by 10%
   Conversion Factor will go from $36.09 to $32.26
   Reduction of Conversion Factor done to maintain Budget Neutrality
   Greatly affects some reimbursements; even with higher wRVU rates
9. Add-on-codes for Prolonged Services

CONVERSION FACTOR AND RVUS. "IN THE BEGINNING", THERE WAS FEE FOR SERVICE

The question is, how did we evolve into our current 2021 Medicare Physician Fee Schedule, or MPFS? Sometimes understanding the past helps us better understand the present. Since the introduction of the 2021 MPFS, there has been an ongoing and focused disputation over the 2021 reimbursements for patient cognitive care verses non-cognitive care. The discussion is in reference to the 2021 10% reduction in the Conversion Factor used in conjunction with RVUs to determine reimbursement for E&M codes. The reduction in the Conversion Factor is coupled with adjusted RVU values for E&M services. The changes significantly benefit some medical specialties but also decreases reimbursements for other medical specialties. But what is the "Conversion Factor" and how did "RVUs" even enter into determining physician reimbursements? Before discussing the impact of physician compensation as related to the 2021 MPFS, it might be worthwhile to see how medicine evolved into mandating "Budget Neutrality" coupled with RVUs and a Conversion Factor, all of which determine which physicians and specialties are considered by some as the 2021 'winners" and which are the "losers" in the 2021 CMS MPFS.

As healthcare expenses continued to escalate during the prosperous post World War 11 economy, the political environment became favorable toward ensuring medical care for senior Americans who were no longer working and did not have employment-based coverage. President Harry S Truman (1945-1953) was the first U.S. President to seek a federal healthcare program to assist senior American citizens. His efforts to develop healthcare coverage for senior Americans was unsuccessful. Several years later, on July 30, 1965, President Lynden Baines Johnson (1963-1969) signed Medicare into law. The bill was signed into law at the Truman Library in Independence, Missouri with former President Truman receiving the first Medicare card.

Initially, under Medicare legislation, physicians were reimbursed according to the "Usual, Customary and "Reasonable Rates". There was no Medicare Physician Fee Schedule (MPFS). Doctors were paid what they charged and billed. That reimbursement plan did not last long. As healthcare expenditures continued to escalate, Congress passed legislation which ultimately restructured the way Medicare reimbursed physicians. In 1992 new legislation established the Medicare Physician Fee Schedule and the newly developed *Resource Based Relative Value Scale (RBRVS)* established a standardized reimbursement/payment schedule. The *Evaluation and Management (E&M)* model was part of the new RBRVS payment system. In addition to a new national fee schedule, updated *Current Procedural Terminology (CPT)* codes were published. The 1995 Documentation Guidelines For Evaluation and Management Services was released. The 1995 Guidelines were revised to include specialty specific physical examinations in 1997. Those "Guidelines" remained the template for reimbursement for E&M services for the past 25 years. But, as will be seen, much is changed in 2021.

The way RBRVS works is as follows. Each medical service is represented by a CPT code. RBRVS attaches a relative monetary value, or *Relative Value Unit*, *RVU*, to each CPT code. The RVU is a numeric value that has been developed to represent three components of each medical service: 1. Physician Work (wRVU), 2. Practice Expense (peRVU) and 3. Medical Liability (mlRVU).

Total RVU= Work RVU + Practice Expense RVU + Medical Liability RVU.

There is also a requirement than any RVU changes be *Budget Neutral* which means that for every additional dollar allocated to a given service there is a dollar less for those who do not use a given code:

← BACK TO PAGE 1
NEXT PAGE →

Total RVUs are then multiplied by a Geographic Cost Index (GPCI)

wRVU x (GPCI) + peRVU x (GPCI) + mlRVU x (GPCI) = Total RVU

A *Conversion Factor* (CF) is determined by legislation every year. The CF is a multiplier which is used to "convert" the geographically adjusted RVU to determine the Medicare allowed payment amount for a particular service. The CF is a fixed dollar amount based upon a complex formula set by statue. The CF incorporates different economic indices as the Medical Economic Index, Budget Neutrality and Legislative Changes, then translates each RVU into a dollar amount. Therefore,

Payment = Total RVUs X the Conversion Factor

2021 REDUCTION OF THE CONVERSION FACTOR: WINNERS AND LOSERS

So, how is this applicable to the 2021 MPFS? Due to the Budget Neutrality mandate, any 2021 increases in Outpatient CPT codes 99202-99205 and 99211-99215 forces CMS to adjust the Conversion Factor in order to counterbalance those increases in code values that CMS implements. Thus, the 2021 CMS MPFS decreases in the Conversion Factor from $36.09 to $32.26 is to maintain Budget Neutrality. For specialties that primarily bill the office and outpatient E/M codes, the magnitude of the RVU increases in these code values outweighs the cut to the Conversion Factor—so overall, those clinical specialties will see an increase in their reimbursements. Conversely, there will be a significant number of physicians who will see reduction in reimbursements under the new 2021 MPFS. For Neurology, there is an expected 6% across the specialty increase in reimbursements with variations depending on the individual provider's practice. Other projected payment increases of between 13% to 17% include endocrinology, family medicine, rheumatology and hematology/oncology. On the loosing side, payment cuts are projected to be between 8% and 11% for others such as surgeons, nurse anesthesiologists, chiropractors, pathologists, physical and occupational therapists, cardiac surgeons and radiologists.

Because of the disparity between "winners' and "losers", the CMS 2021 Physician Fee Schedule's budget neutrality requirements appears to shift funds from one specialty to another which many colleagues believe is an inappropriate discrimination among physician specialties. Cognitive E&M visits have historically been undervalued as compared to procedural visits, a factor which was presumably weighed when the 2021 MPFS was being developed. There are many physician colleagues and organizations who believe that if CMS cannot obtain a budget neutrality waiver from Congress, there should then be a delay in implementation of the revaluation of E/M and related code visits and the 2021 MPSF should be rolled back to 2020 values.

We neurologists have all received recent emails and communications from The American Academy of Neurology related to this issue. While most neurologists will receive a significant benefit starting in 2021 with a 6% overall increase for E&M services, because of budget neutrality there will also be an across the board cut to all other services. Indeed, some neurologists may experience payment reductions if they provide few E/M services. Thus, along with a number of other societies, the AAN is supportive of efforts to waive budget neutrality to offset cuts to reimbursements for non E/M services but the AAN also believes that any actions to waive budget neutrality should not result in a delay or in any way undermine CMS's decision to fully implement the new E/M payment structure on January 1, 2021. Other societies and industry organizations continue to argue that E/M payment increases should not be offset by rate decreases for other services covered by the Medicare Physician Fee Schedule. Many organizations have urged CMS to work with Congress to stop penalizing doctors with the current budget neutral methodology. In an October 5, 2020 letter to Seema Verma, MPH, Administrator Centers for Medicare & Medicaid Services, from 1.4 million physician and non-physician practitioners throughout the country, representing 47 different societies, academies, associations and other professional medical organizations that signed the letter, there was strenuous objection to the budget neutrality reduction proposed by CMS in the 2021 MPFS. At the time of the writing of this report, there is much legislative and political activity regarding 2021 reimbursements for E&M services. We will wait and see the outcome but until then, for 2021, the CMS MPFS will include a 10% cut in the Conversion Factor.

HISTORY AND PHYSICAL EXAMINATION: NO LONGER NECESSARY?

For the past 25 years, the 16-page CMS 1995 and 49-page 1997 Medicare Documentation Guidelines For Evaluation and Management Services defined the details of how to meet the Medicare rules and regulations of E&M CPT coding. The 25-year-old and 23-year-old documents identified the (1)History, (2)Physical Examination and (3) Medical Decision Making as the three *Key Components* that required specific documentation guidelines to meet the requirements of CPT E&M coding as well as to determine the level of care provided. Time, which is face-to-face time, could be used for the level of E&M services when Counseling and/or Coordination of Care dominate greater than 50% of the encounter. Under the revised Medicare E&M Guidelines, which will take effect January 1, 2021, physicians will chart and select codes entirely based on *either* Time spent with the patient *or* Medical Decision Making. Prior historical key elements to define the E&M level of service provided, as defined in the 95/97 CPT E&M Guidelines, including the History and Physical Examination, will still be conducted but as and when deemed *medically appropriate* by the physician.

Thus, starting January 1, 2021, physicians and other professional providers, will bill for the level of outpatient E/M services based on *either* the newly revised MDM guidelines *or* Total Time. Total time will be counted as total time spent with the patient on the day of service, including non-face-to-face services. The History and Physical Examination will be elim-

← BACK TO PAGE 1 NEXT PAGE →

inated as a key element for the level of code selection, but the medical encounter should still include a *medically appropriate* history and/or physical examination, when performed. The nature and the extent of the history and/or physical examination is to be determined by the treating physician or other qualified health care professional reporting the service. The care team may also collect historical information which may come from the patient, caregiver, by portal or questionnaire or obtained from other professionals in the office, including nurses, APPs and MAs. That patient information, which was previously the key element of the History, can be reviewed by the reporting physician or other qualified health care professional and then documented in the medical record as having been obtained and reviewed. Not being required to again perform and record a detailed and complete physical examination and neurological examination for a healthy 20 year old established patient being seen for routine headache follow up is clearly realistic and appropriate. However, while the H&P is no longer a key component in code selection or defining the level of the E&M encounter, appropriate documentation of important information in the medical records, when indicated, is still an important component of the patient's clinical evaluation. As the saying goes, "if it was not documented, it was not done". Documentation of appropriate historical information and/or physical examination is still a main line of defense in any medical legal matter.

MEDICAL DECISION MAKING 2021: COMPARED TO THE PAST IT CAN ONLY GET BETTER!

Medical Decision Making MDM) refers to the *Cognitive Complexity* of establishing a diagnosis for selecting a management option. MDM includes integration of a provider's knowledge and experience with the history, physical examination, laboratory data and other data into a process of formulating and developing a treatment plan. MDM considers the (1)number of diagnostic and management options considered and (2)the complexity of data analyzed. MDM also incorporates (3)the level of risk to the patient within the decision making process. The risk includes that of significant complications, morbidity and/or mortality, as well as comorbidities associated with the patient's care. MDM is an assessment of not only the risk of the disease being treated but also the risk of selecting diagnostic procedures and management options, both during and following procedures or treatment.

Medical Decision Making was a new E&M coding requirement formally introduced in the 1995 CPT E&M Documentation Guidelines. While the 1995 and revised 1997 E&M Documentation Guidelines had clearly defined numerical values for the History and Physical Examination, the first two key components of CPT E&M coding, with the introduction of MDM, physicians and other health care providers were asked to quantify the "amount" of data and at the same time define the "complexity" of data required for MDM documentation with insufficient MDM coding instructions. The CMS measures did not provide specific direction in the 95/97 E/M Guidelines to quantify the data or to make these numerical determinations. There were no obvious quantifiable MDM parameters in the Guidelines to help meet compliance.

The MDM Table on page 43 of the 1997 revised E&M CPT Guidelines was the template for MDM coding but the text provided no clearly defined formula for how to use or navigate the table. Thus, while the 95/97 Guidelines supplied numerical values to determine the level of History and Physical Examination performed, MDM documentation essentially referred to "Qualitative" metrics without providing "Quantitative" metrics of measurement. There were no definitions in the MDM Table nor in the MDM descriptive text to help explain what "Minimal", "Limited", "Multiple", or "Extensive" specifically meant related to a diagnosis nor what "Amount" and "Number" meant in numerical quantitative measures. Subsequently different MDM Scoring System methodology had been developed by private organizations and while none were officially endorsed or validated by CMS, certain scoring systems became the "industry standard". As an example, one of the most commonly used scoring systems was the independently developed Marshfield Clinic Scoring Tool which became the template for most other MDM scoring systems nationally.

There has been much momentum to simplify Medicare CPT E&M coding over the years. It was thought the EHR would make documentation easier and more standardized, but the issues with EHR, including documentation and coding, also frequently included templates which maximized H&Ps and even MDM levels of care to the highest levels of codes for service provided. The number of level 4 and level 5 codes submitted for reimbursement has greatly increased over these last few years. In addition, the physician administrative burden of documentation and coding and additional physician time spent on data entry and meeting the various coding rules and regulations was for many, laborious. Since E/M services represent approximately 40% of the billed charges annually, there is much incentive to maximize the efficiency and accuracy related to E&M coding and subsequent provider reimbursements. After much focused negotiation in 2019 and 2020 between the CMS and the AMA and other medical industrial representatives, it was agreed that the most efficient and effective way to define the reimbursable components of an E&M doctor/patient encounter was to allow physicians to choose whether to document the visit based on restructured Medical Decision Making or *Total* Time with an H&P not included in determining the level of the code but defined as *appropriate* for the encounter.

The agreement between CMS and the AMA which led to the 2021 MPFS was a monumental undertaking. In response to the initial CMS proposal to "collapse" and "blend" CPT level of service codes 2 – 4 into one total payment amount, a change which would have resulted in significant economic loss for numbers of physicians, the chairs of the AMA CPT Editorial Panel and the AMA Relative Value Scale Update Committee (RUC) created a 12 member CPT/RUC Workgroup of E/M. In addition to the 12 Workgroup Members, about 300 stakeholders from National

← BACK TO PAGE 1
NEXT PAGE →

Medical Specialty societies participated in the decision making process In addition to changing the definition of "Time" from "Typical Times" to "Total Times" associated with each E&M CPT code, the entire MDM Guidelines were redeveloped and updated with criteria being made specific to the individual E&M office visits codes 99202-99215. While the Workgroup did not materially change the three current MDM sub-components listed in the 95/97 Documentation Guidelines, there were extensive edits to the elements for code selection and numerous revised criteria clarifying definitions which were not clearly defined in the 95/97 Guidelines.

The new 2021 MDM table used for E&M coding features a redesigned format. The ambiguous terms are replaced with more descriptive language. The data elements in the old table were re-defined and coding moved away from adding up tasks to now focusing on tasks that actually affect the management of the patient. Where the old MDM table was driven by formulating a complicated point system derived from the *number* of diagnosis or treatment options and the *amount and/or complexity* of data reviewed, the 2021 MDM table will use improved guidelines to help code the level of service performed as correlated with each E/M encounter. The "Risk" component of the 2021 table does still use similar nomenclature as found in the "Table of Risk" on page 47 of the revised 1997 Guidelines, but the terminology is more clearly defined and more applicable to the actual patient encounter.

To navigate the new 2021 level of MDM table properly, the physician or other healthcare providers will need to learn and understand the CPT's definitions for different terms. For example, knowing the MDM definitions for terms as *problem addressed* and what a *self-limited or minor problem* as compared to problems of *moderate or high complexity* will be mandatory for the accurate selection of the proper level of service performed. Providers will need to comprehend the different levels of *risk* as applied to MDM and different levels of risk as applied to treatment and management options such as drug therapy which may require intensive monitoring for toxicity. Other terms as *morbidity* as applied to the definitions of *acute and chronic* illnesses which themselves are referenced in a variety of ways in the "Number and Complexity of Problems Addressed" column.

Another important part in using the new 2021 MDM Table is that simply selecting a diagnosis from a drop-down menu will not be applicable. Compliance for the diagnosis and management portion of the new table will require that physicians and other healthcare providers link each MDM diagnosis with some type of action, be it a prescription, a test, counseling or some other patient related function. Stating that the diagnosis is being managed by another provider will not meet the new MDM compliance rules.

While some of the above 2021 MDM requirements may seem daunting or labor intensive to some, the key, as outlined above, will be to learn how to navigate the newly revised AMA Medical Decision Making Table and to understand the definitions of the terminology used in the table. While much of the terminology is derived from the earlier 95/97 E&M Guidelines, a precise understanding of the thirteen or fourteen important terms used in the AMA Table will be needed to be compliant when using MDM for E&M coding services. There are excellent resources for learning how to use the new table on the AAN website, the AMA website and the CMS website. A printable copy of the revised AMA MDM Table can also be found on those websites as well as on line. In addition, there are case studies and tutorials which can be found at aan.com/EM which illustrate examples of billing using MDM or Total Time.

TOTAL TIME: IT'S ABOUT TIME!

To finally be financially compensated for the non-face-to-face time physicians have been spending on behalf of their patients and in the care of their patients is something many colleagues feel is long overdue. While the inclusion of time has been part of the 95/97 E/M Guidelines, it was only recognized if the time spent was greater than 50% of the visit was face-to-face-time spent in Consultation and Coordination of Care. Starting in January 2021, Total Time may be used to select a code level in office or other outpatient services whether or not counseling and/or coordination of care dominates the service. Total time will include both face-to-face and non-face-to-face time that the physician or other healthcare provider personally spends before, during and after the visit.

The total time spent on patient care does not need to be consecutive but is cumulative time within the day of the patient's visit starting 12:00 am and ending 11:59 pm. Thus, the discussion of a patient with the referring physician the day before the consultation or reviewing an MRI with the Neuroradiologist the day after the visit would not be included in Total Time because it would be outside the 12:00 am – 11:59 pm window. Other such things as having the patient wait in the office for their eyes to dilate for a funduscopic examination would also not fit the definition of Total Time.

In addition, services that are done separately, such as an EMG or the interpretation and reporting of the EEG on the same day would not apply toward the E/M level because separate CPT codes exist for the test or procedure and the actual E&M visit. To bill a code for the performing the tests and interpreting the results plus charge an additional E&M visit code for the performance and interpretation of those tests on the same day would be considered "double dipping". A shared or split visit, which is defined as a visit in which the physician and other healthcare professional(s) jointly provide the face-to-face and non-face-to-face work related to the visit, the time spent by the physician and the other healthcare provider(s) in assessing and managing the patient's visit, is summed together to define total time. Thus, when two or more individuals act together as within a team provider approach to patient care, only the time of the one primary provider, usually the physician, should be counted. Conversely, if a test or study is independently interpreted in order to manage the patient as part of the E/M service, but is

← BACK TO PAGE 1
NEXT PAGE →

not separately reported, that service may be considered part of Medical Decision Making under " Amount and/or Complexity of Data to be Reviewed and Analyzed". Also, Total Time does not include staff time.

Other examples of time based billing on the day of service would include:

- Preparing to see the patient (eg., review of the chart and tests)
- Obtaining and/or reviewing separately obtained history
- Performing a medically appropriate examination and/or evaluation
- Counseling and educating the patient/family/caregiver
- Ordering medications, tests or procedures
- Referring and communicating with other healthcare professionals (when not separately reported}
- Documenting clinical information in the electronic or other health record
- Independently interpreting results (not separately reported) and communicating results to the patient/family/caregiver
- Care coordination (when not separately reported)

Keeping track of the total time spent on behalf of a patient's care on the entire day of the visit could be burdensome. While some EHRs have timers that automatically track when you are logged in to a patient's chart, most systems that have this feature ae still far from perfect. But in most E&M instances, the complexity of the patient's visit is often clear relatively early in the encounter. Also, different Neurologists have variable times allotted to new patient visits and established patient visits. Generally, on an average, new patient visits for Neurologists will range from 30 minutes to 60 minutes while an established visit will range from 15 minutes to 30 minutes. While, under the current 2021 E/M rules and regulations physicians are not required to itemize their time spent with patients, it is reasonable to anticipate that in the future there may be some type of documentation that will be required, presumably utilizing the EHR. But to date, and at the time of writing this report, actual documentation of the time spent in calculating Total Time for the E&M level of the patient encounter is not a requirement.

The table below itemized the 2021 Total Times established for the four New Patient Codes and the five Established Patient Codes. It would pay to get familiar with the following table which defines total time for CPT 99202-99215

New patient code	Tota time (2021)	Established patient code	Total time (2021
99202	15-29 minutes	99211	N/A
99203	30-44 minutes	99212	10-19 minutes
99204	45-59 minutes	99213	20-29 minutes
99205	60-74 minutes	99214	30-39 minutes
		99215	40-54 minutes

PROLONGED SERVICE CODES. HOW DID IT GET SO LATE SO SOON?

Before discussing the 2021 E&M "add-on-codes", it is first important to briefly review some of the terminology. The Healthcare Common Procedure Coding System is referred to as HCPCS. The HCPCS is divided into two principle subsystems. The two systems are referred to as Level 1 and Level 11.

Level 1 of the HCPCS constitutes the Current Procedural Terminology or CPT numeric coding system which is maintained by the American Medical Association. The AMA also publishes the CPT Codebook that is in most physician offices. The second level, Level 11 of the HCPCS, is a standardized coding system that is primrily used to identify products, supplies, and services not incuded in the Level 1 codes. Level 11 codes include such things as ambulance services and durable medical equipment, prosthetics, orthotics and supplies when used outside of a physician's office. G-codes are also a part of the HCPCS national Level 11 code set. G-Codes are temporary codes that are assigned to services and proceedures that are under CMS review before being included in the CPT coding system. G-codes are used to identify professional health care procedures and services that would otherwise be coded in CPT but for which there are no CPT codes. While G-Codes are similar in function to CPT codes, they are separate codes managed and used by The Center for Medicare and Medicaid Services (CMS). The G-Codes allow CMS to bring a service forward quickly and support a service that the AMA CPT committees have not yet moved forward with supporting. G-Codes may also be used if CMS is not entirely happy with the way CPT has defined a service or how the CPT code is structured. In addition, G-Codes allow CMS to foster innovation as deemed appropriate by CMS.

The AMA has developed a new CPT Prolonged Service Code divided into 15 minute intervals of prolonged care. The new code is to be used when Total Time is chosen as the CPT reporting option. As with all other Total Time parameters, the 15 minute prolonged service code can only be used on the same day of service. The new code is *99417*. However, CMS does not agree with the designed uses of the AMA prolonged service code 99417 and developed their own HCPCS prolonged service code. The CMS code is a G-code, *G2212*. The guidelines for using either code, 99417 or G2212, require reporting the codes with CPT level 5 codes 99205 and 99215.. Both codes only reflect clinician time as opposed to staff member time and again, are to be used when Total Time is used to select the code. Medicare will not accept the AMA 99417 code. We currently do not know if private insurance companies will accept the CMS G2212 code. As a general rule, private insurance companies prefer not to deal with G-codes. There are some differences in how 99417 will be used as compaed to G2212.

99417 vs **G2212**: When using 99417, the total time of 15 minutes must be met to report this code. Midpoint times,

← BACK TO PAGE 1
NEXT PAGE →

such as 7.5 minutes, will not be accepted. The entire 15 minutes must be done in order to add on 99417 for prolonged services.

When using 99417, the code can be selectd *after* 75 minutes or longer for new patients where 99205 is 60-74 minutes or at 55 minutes for establshed patient code 99215 where the time range is 40-54 mintes. For some private payers, it appears that 99215 may be added to the lower end of the level 5 code. However, the CMS rule for using pronogned service code G2212 does not agree with CPT. For CMS, code G2212 cannot be used until *after* the first 15 minutes *is actually added* to the maximum time in the time range. So, in order to bill a Medicare prononged service code G2212, the clinician must *first meet 15 minutes* of addditional tme to the maximum time in the time range. Thus for using the CMS G2212, if adding to a new patient code 99205, the total time required for reporting would start at 89 minutes and for code 99215 which ends at 54 minutes, G2212 could be reported at 69 minutes. The wRVUs for G2212 are 0.61 which would translate int about $31.40 payment for a national non-facility payment and about $30 for a national facility payment

CPT Code using 99417	Total Time Required for Reporting
99205	60-74 minutes
99205 x 1 and 99417 x 1	75-89 minutes
99205 x 1 and 99417 x 2	90-105 minutes
99205 x 1 and 99417 x 3 or more	105 minutes or more

CPT Code using 99417	Total Time Reqired for Reporting
9215	40-54 minutes
99215 x and 99417 x 1	55-69 minutes
99215 x 1 and 99417 x 2	70-84 minutes
99215 x 1 and 99417 x 3 or more	85 minutes or more

CPT Code using G2212	Total Time Required for Reporting
99205	60-74 minutes
99205 x 1 and G2212 x 1	80-103 inutes
99205 x 1 and G2212 x 2	104-118 minutes
99205 x 1 and G2212 x 3 or more	119 minutes or more

CPT Code using G2212	Total Time Required for Reporting
99215	40-54 minutes
99215 x 1 and G2212 x 1	69-83 minutes
99215 x 1 and G2212 x 2	84098 minutes
99215 x 1 and G2212 x 3 or more	99 minutes or more

SUMMARY. A LOT OF STUFF BUT HOPEFULLY WORTHWHILE

Well, there you have it! There is obviously a great deal more to learn about the new 2021 E&M Medicare Physician Fee Schedule. But at this point, an attempt was made to focus upon some of the key components that will need to be mastered to initiate the use of the new guidelines, starting on January 1, 2021. To compliment the data in this report, the reader is again encouraged to go to aan.com/EM as well as the AMA CPT E/M webpage and CMS website where additional information on the new 2021 Guidelines can be found along with the new AMA MDM Table. Additional recommendations are for the practice to check with the EHR vendors to see what changes in programing may be recommended for readiness. It would also be worthwhile for the practice to review existing practice protocols such as the ability to meet the new MDM Guidelines and Total Time, and to model the new changes in coding to identify if there will be any impact to the practice reimbursement. An example to the later would be to examine current total times spent per encounter on the day of service and attempt to identify the typical level of complexity, using the new AMA MDM Table, in anticipation of any changes in the level of billing. The later includes noting how many patients each provider should see with the new emphasis on MDM and Total Time.

Also, the Billing and Coding staff will need to be educated on how to use the AMA MDM Table. It may also be worthwhile to contact the practice's primary payers to see whether they will adopt the new 2021 MPFS. We really have no information to date but it is possible that some private payers may continue to require code selection based upon the original E&M three components: History, Physical Examination and MDM; or they may have specific requirements as they too try to navigate the new E&M coding system. It may also be productive to review some of the practice's current patient records to see whether the data entry would support the information needed in the new MDM Table and cross check the level of E&M charged prior to January 1, 2021 with that in the new Table.

Finally, there were other E&M CPT codes which were not reviewed in this report, such as 99358 and 99359 for prolonged services on a date other than the date of the face-to-face encounter. Currently these codes must pertain to a face-to-face encounter that has occurred or will occur related to ongoing patient treatment. It appears that these codes, along with some others, are probably also undergoing review and in reviewing the literature, the status of different codes is still being determined. Thus, the focus in this report was on those codes which will be used by the majority of neurologists starting January 1, 2021.

← BACK TO PAGE 1
NEXT PAGE →

A new differential? From ischemic stroke to failed extubation – considering COVID-19 when assessing acute neurological symptoms

Jonathan Paul Donnelly, MD, MRCP(UK), Department of Neurology, University of Texas Health Science Center San Antonio, Resident

With the constant flow of new information about SARS-CoV-2, and how it seems to affect every organ system in one way or another, it is difficult to know exactly what we should be looking for. When this virus first reared its head as another respiratory illness, many Neurologists likely did not take too much notice, outside of personal fears about how it could affect them or their loved ones. However, it increasingly became clear that this was no ordinary "viral URI" that we may have seen often back when we rotated in the ER as interns. This is not only regarding how it rapidly spread across the globe, infected millions, and forced entire nations into historic levels of lockdown, but how it was clearly not confined to the respiratory tract. With reports of anosmia, hallucinations, vasculitis, even "covid toes", the various manifestations of the disease seemed endless. As case reports of unusual neuro presentations started to increase in number and variety, it became obvious that Neurologists could no longer sit by the sidelines; this virus had invaded their specialty too.

The impact of coronavirus on Neurology practice is multi-layered. The fear was that patients with conditions such as epilepsy, Parkinson's disease or ALS would experience acute decompensation of their illnesses, and that was how Neurologists would end up caring for patients infected with the virus. The reality is that the virus has hit the nervous system in unexpected ways. Suddenly, young healthy patients diagnosed with encephalitis, ischemic stroke, and Guillain-Barre syndrome were testing positive for COVID-19. Furthermore, some of these patients did not even have preceding infective symptoms like shortness of breath or fever, which might have tipped off the consulting Neurologist that they were dealing with a COVID patient. Worse still, in the hyperacute setting, when responding to stroke alerts, the shadow of coronavirus hangs over the neurology resident who, in the midst of trying to calculate an NIHSS, make quick decisions about tPA and organize swift investigations, also now has to think about the possibility that the patient they are trying to rapidly assess is a carrier of this disease. With more rapid testing still on the horizon, ruling out COVID-19 before making the time-sensitive decisions about tPA or even thrombectomy is not feasible at this stage. Screening questions are also not ideal with the aphasic or unconscious patient, and families are often left behind due to visitation restrictions. The other option is to don PPE for every stroke alert, although this then runs into institutional issues of PPE policy and availability. In the post-acute phase, the question of the virus can linger. Often in our young patients we look for unusual, inflammatory causes for why an otherwise healthy person without vascular risk factors would have a stroke. Should COVID-19 be on that differential now? Should it be on the differential for every stroke patient, even if they are elderly with diabetes and hypertension?

Just as SARS-CoV-2 seems to have seeded into numerous aspects of daily life, it has made its way into the daily routine of the Neurologist. For the Vascular neurologist presented with an atypical vasculopathy causing stroke, maybe ask the patient again about recent sick contacts and travel history. For the Neuro-intensivist having difficulty weaning a Guillain-Barre patient from the ventilator, maybe that preceding febrile illness was something other than Campylobacter. For the consultant general neurologist asked to see a patient with acute ataxia or cranial neuropathy, take another look at that chest x-ray in the ER. The novel coronavirus has made its way into the list of differential diagnoses for new neurological complaints, even in the absence of typical respiratory symptoms, and this is likely to remain the case for an exceptionally long time.

← BACK TO PAGE 1
NEXT PAGE →

Arun Nagaraj, MD

Fragile X Ataxia Syndrome Misdiagnosed as Multiple Sclerosis. A Case Report and Review of the Literature

Arun Nagaraj, MD, Texas Neurology and Raphael Schiffmann, MD, Baylor Scott & White Research Institute, Dallas

Raphael Schiffmann, MD

BACKGROUND

Fragile X Ataxia Syndrome (FXTAS) OMIM#300623, is a genetic disorder caused by a mutation in the FMR1 gene inherited through an X-linked mechanism with incomplete penetrance. This is a distinct entity from Fragile X Syndrome. Fragile X Syndrome is primarily a pediatric disorder whereas FXTAS occurs in late adulthood. The symptoms and MRI abnormalities of FXTAS overlap with many other disorders which can make it difficult to diagnose. It is important for neurologists to be aware of this condition and its diagnostic criteria.

CASE REPORT

A 60-year-old male diagnosed with multiple sclerosis was seen in May 2019 for a second opinion regarding MS. Symptoms started approximately 13 years prior when he had intense right shoulder pain and neck spasms. He had shoulder surgery which did not help. He then developed symptoms of right arm weakness and tremors 1 or 2 years later. At that time, he believed he had a middle cerebellar peduncle lesion. He saw an MS specialist who diagnosed him with clinically isolated syndrome. The results of his lumbar puncture were reportedly normal.

He developed gradually progressive intentional tremors and pain. He described a constant dull muscle ache, worsened by exertion. He suffered progressive imbalance with two or three falls in the previous year. He saw two more MS specialists who concurred on the diagnosis of MS and he was started on ocrelizumab in 2018. Although he felt it may have helped subjectively, he had infusion reactions causing pain and spasms resulting in an ER visit. Overall he felt his symptoms continued to gradually worsen.

His neurological exam was notable for prominent bilateral intentional tremor and ataxia on finger to nose assessment. His gait was wide-based and mildly unsteady. He also had pes cavus bilaterally. Brain MRI findings from April 2019 are shown in figure 1. The fragile X ataxia genetic test was ordered, the results of which showed 107 CGG repeats in the FMR1 gene (Mayo Clinic Laboratories).

The patient's mother requested to be tested as well. She is 89 year old who is generally in good health, ambulating without any gait assistance. She has had a mild left sided intention tremor and chronic neck pain. The results of her genetic testing showed 60 CGG repeats in the FMR1 gene.

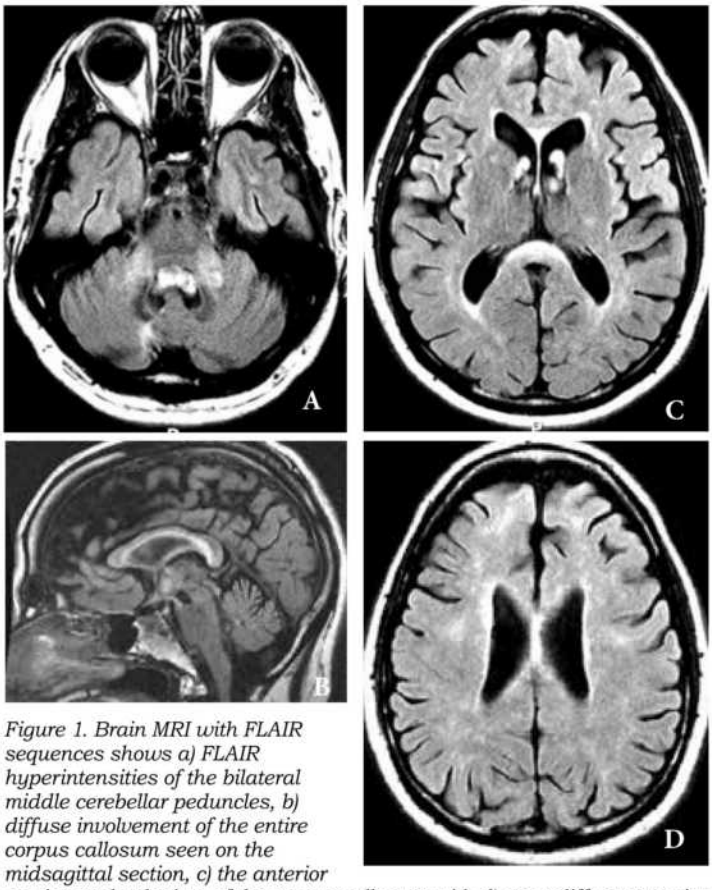


Figure 1. Brain MRI with FLAIR sequences shows a) FLAIR hyperintensities of the bilateral middle cerebellar peduncles, b) diffuse involvement of the entire corpus callosum seen on the midsagittal section, c) the anterior portion and splenium of the corpus callosum with d) more diffuse superior subcortical white matter involvement.

FXTAS CLINICAL FEATURES

Typical symptoms of FXTAS include ataxia, neuropsychiatric symptoms, and intentional tremor. Neuropathic pain is also common and is often an early symptom as well. This is sometimes associated with neuropathy. This pain is frequently debilitating and can be mislabeled as fibromyalgia.

Cognitive decline and memory problems are often seen. Depression can be severe. Symptom onset is variable and typically gradual in nature. In one case series, the average age of symptom onset for FXTAS was 60.6 years.[1] Other associated findings include parkinsonian features, vertigo, and tinnitus. Prognosis is variable and the median life expectancy after symptom onset in one review was 21 years.[6] Higher CGG repeat length/repeat number correlates with worsening severity of ataxia. [7]

← BACK TO PAGE 1
NEXT PAGE →

EPIDEMIOLOGY

FXTAS is much more common in men as it is an X-linked disorder with incomplete penetrance. 40-70% of males who carry the FMR1 premutation will develop symptoms while only 16-20% of females who carry the mutation will become symptomatic. Approximately 1 in 150-300 females and 1 in 400-850 males are carriers for the mutation. [2, 3]

PATHOPHYSIOLOGY

The FMR1 premutation results in a toxic gain of function of mRNA. There is an excess of CGG trinucleotide repeats ranging from 55-200 in the FMR1 gene that causes FXTAS. The exact molecular mechanism for the neurologic pathology is unclear. In contrast, Fragile X Syndrome (FXS) involves methylation of the FMR1 gene with loss of expression of this gene and has a very different phenotype from FXTAS.[3]

DIAGNOSTIC CRITERIA

Established diagnostic criteria for FXTAS is summarized in table 1.[2] In order to be grouped into this table, patients must have the confirmed premutation of the FMR1 gene. In order to meet criteria for definite FXTAS, patients must have confirmed premutation of the FMR1 gene (55-200 CGG repeats) along with one major radiological abnormality and one major clinical feature. Signal abnormalities with FLAIR or T2 hyperintensities in the middle cerebellar peduncles on brain MRI (MCP sign) should raise suspicion for FXTAS as this is a major radiological sign. White matter lesions in the splenium of the corpus callosum are often seen as well which is considered a minor radiological sign.

Radiological	
Major	MRI white matter lesions in the MCPs and/or brain stem
Minor	MRI white matter lesions in the cerebral white matter
Minor	Moderate to severe generalized atrophy
Symptoms	
Major	Intention tremor
Major	Gait ataxia
Minor	Parkinsonism
Minor	Moderate to severe short term memory deficits
Minor	Executive function deficits

Table 1: Diagnostic requirements for FXTAS. Positive genetic testing with the FMR1 premutation is a prerequisite for consideration. A definite FXTAS diagnosis requires one major radiological finding plus one major symptom. Probable FXTAS diagnosis can be made on the basis of either one major radiological sign plus one minor clinical symptom or two major clinical symptoms. Possible FXTAS diagnosis can be made with one minor radiological sign plus one major clinical symptom.

DISCUSSION

It is easy to misdiagnose FXTAS because it presents with such a wide variety of symptoms. One retrospective chart review describes that Parkinsonism and idiopathic Parkinsons were the most common misdiagnoses for FXTAS although a large variety of other misdiagnoses were given including possible MS and myasthenia gravis.[4]

In the case presented here, initially the middle cerebellar peduncle lesion was likely unilateral and then on subsequent follow up imaging it was bilateral. The middle cerebellar peduncles and corpus callosum can be affected in both MS and FXTAS.[5] However the confluent nature of the lesions along with the symmetry of the abnormalities seen on MRI in this case are not typical for MS. Although there are currently no disease modifying or gene therapies available for FXTAS and Fragile X syndrome, early diagnosis can be helpful as genetic counseling can be offered.

CONCLUSIONS

It is important for neurologists to be aware of FXTAS. It is often misdiagnosed because it can mimic other conditions including MS, Parkinsons Disease, and small fiber neuropathy. Symmetrical T2 hyperintensities in the bilateral middle cerebellar peduncles seen on brain MRI should raise suspicion for this condition. Genetic testing is becoming increasingly more accessible.

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← BACK TO PAGE 1 NEXT PAGE →

Dynamics of the Brain

David B. Rosenfield, MD

Chair, Speech and Language in Neurology, Director, Speech and Language Center, Director, EMG and Motor Control Laboratory, Stanley H. Appel Department of Neurology, Neurological Institute, Houston Methodist Hospital, Professor, Weill Medical College of Cornell University

Ergodic Theory, a component of probability theory, posits that if one wants to study particular dynamic systems that are changing in time, one can study over time the long-term average of that system or investigate simultaneous different internal components within that system at different points in time, and the two analyses are equally valid. Broadly speaking, it contends that behavior of a dynamic system averaged over time equals the assessment of all subsets within that same system at any one point in time. Or, more simply, if you study a patient with a disease (e.g., a dynamic system) throughout their life, that is equivalent to studying several people with the same disease at different stages of the disease during their lives.

In other words, case reports can have merit.

Hubert H Humphrey, the late Senator from Minnesota and one-time Vice President candidate, contended that a society, which is certainly a dynamic system, is defined by how it treats its elderly, sick and children. A continuum exists within any society, from birth to old age, with many stations in between and each person functioning as an independent, cohesive, intra-person dynamic system, some being sick, some healthy, others young, some old, all at different stations in their individual life cycles.

How an individual travels through these separate life cycles alters as well as reflects who they are, what they become, what they want to become and even what they hope not to become. And, the transit of these individuals all transpire respectively within their individual societies.

In other words, the dynamic system of a person interacts with dynamic systems of other persons and, together, they form a society. These persons can individually change, the society that they form can change and all ongoing interactions can change, everything affecting everything else.

As inferred from above, one can study a society, which is a dynamic aggregate of individual people and their individual human brains, by analyzing what happens to any particular individual throughout their life cycle's journey or study several individuals at different stages in their respective life cycles. But, how do changes evolve? Since the society reflects the ongoing dynamic of the individuals, is it one person or several persons that cause the change? Do changes come from bottom-up dynamics (e.g., people making changes that affect the larger whole: society) or do changes come from top-down interactions (e.g., aggrege society makes changes that then affects individuals) or both?

Digesting history, changes can occur for several reasons. One of the most forceful vectors for change reflects how the dynamic of the society affects the dynamics of the individual and how that in turn affects the society itself.

Certainly, we all recognize that different things happen to different people at different times: Some may become marginalized (e.g., the system recognizes them but puts them aside, without significant power), which produces dangerous isolation. Yet, others may be totally ignored, which usually results in smug indifference. Either way, the dynamic of each group affects the society.

This holds on all levels for just about anything. Consider the marginalization of (non-ignorable) bacteria into the human organism, the former eventually being absorbed into eukaryotic cellular structure, becoming mitochondria and now performing valuable functions for the organism. Or, consider those who are ignored, as are physicians in most hospital administrative systems, resulting in physicians often having a de facto smug indifference toward administrators.

Either way, changes result from these interactive dynamics, the bacteria now producing ATP energy from their mitochondrial state or the effects on health care from what has happened and is happening to physicians.

Either way, one organism's total journey tells a lot about that organism (human being or bacteria), where they are, where and how they live(d) their lives and also about the society in which they live.

Within this milieu, some might query the value of being "anti-fragile," ala Nassim Talib, referencing individuals and societies benefiting from instability, whereas others digest this solely as part and parcel of the human condition. Regardless, the ergodic filter permeates the dynamic space and allegedly renders it amenable to study.

Thus, case reports have meaning.

We neurologists investigate and deeply entwine with this labyrinth of development and change. Without getting into the argument that physicians may well be among the last true professionals (e.g., who else would perform their duty sometimes for

← BACK TO PAGE 1 NEXT PAGE →

free?—try that with a roofer), we ponder these questions all within an equation of what is the brain doing and what is being done to or within the brain.

But, as professionals of the brain, we recognize that there are overlapping dynamic systems within the same cerebral space. We can extend this query to whether the dynamic of how a brain processes language equates to the dynamic of how it looks at the world, thinks, prohibits expansion from a paroxysmal depolarization spike into a clinical seizure or how it fights an initial attack of demyelination.

Societies, reflecting their dynamic interchange of multiple human brains, orthogonally interact on axes of politics, economics and social norms, just as brains have their axes of physiology, anatomy and neuropharmacology, as well as others. The interactions of these organs produce or certainly contribute to society and concurrent civilizations with their always changing dynamic interactions and nothing remaining a constant.

Consider the Olympic Games, a robust interaction between different international societal realms. Many contend that Olympic Games have their own dynamic and individuate from the political dynamic. However, since 424 B.C.E., when Sparta fought Athens in the Peloponnesian Wars and was sequestered from the Olympiad, politics and Olympic Games interact. Fast forward to 1988, when Pyongyang sought to stop Seoul's planned hosting of the Summer Games by exploding a South Korean passenger jet, killing over 100 people. Now, in 2018, the two nations, through the Olympics, have a new social discourse blending politics and sports.

One might contend that the two nations are remotely akin to cerebral hemispheres in their own alleged dynamic space, possibly representing the thesis that there remain vast overlapping systems whether in the world of socio-economic-political processes or overlapping dynamic systems within the brain itself.

Returning to the individual, when part of one's brain does not want to go to a party because that individual has no friends and will feel alone, and another part of the brain then decides to stay at home, contributing to that person not developing friendships, this dynamic interplay highlights a neurosis, wherein an individual's defense mechanisms work against their own well-being.

Some poets or members of the literati might contend that countries and societies are merely individual brains on steroids or in drag. But, what about the actual brain?

Although one can argue that the science of mathematics is also a form of philosophy and that probability theory offers much to be discussed, we must query whether the brain is a lot more than a computer as it covers these myriads of simultaneous dynamic spaces and has its own filters, the combination of all of which we call, "Neurology."

Annual Winter Conference – A VIRTUAL Experience

Padraig O'Suilleabhain, MD, Program Director, TNS 2021 Winter Conference

For the 2021 TNS Winter conference you can as usual expect a stimulating series of talks from a diverse group of dynamic speakers from around the state and the nation, covering the breadth of clinical neurology practice. There are twenty 50-minute lectures: some are broad reviews and overviews, while others address niche topics.

In response to the pandemic, the conference format is virtual. Lectures are being recorded, and will be posted online in mid-January, for an a-la-carte viewing at your convenience. On Saturday, February 6th, from 9:00 – 2:00 pm (CST), there will be a live interactive session, during which the speakers will be available for Q+A. AAN President- elect, Dr. Orly Avitzur, will, also, deliver a keynote talk about the future of neurology.

For this conference, we are offering 2 hours of self-assessment CME in addition to 25.25 hours of standard CME. The SA-CME can accumulate toward your ABPN maintenance of certification. To claim the SA-CME, you will take a pre-test before viewing the lectures followed by a post-test after the conference.

We look forward to sharing the upcoming conference with you in virtual format, and, also, to when the TNS membership can meet again in person for educational and social purposes.

← BACK TO PAGE 1 NEXT PAGE →



Sarah Fredrich, MD Kyle Blackburn, MD Lauren Tardo, MD

Multiple Sclerosis Disease Modifying Therapy Review: 2019 - 2020

Sarah Fredrich, MD, Autoimmune Neurology Fellow, Department of Neurology, UT Southwestern Medical Center

Kyle Blackburn, MD, Assistant Professor, Neuroimmunology division, Department of Neurology, UT Southwestern Medical Center

Lauren Tardo, MD, Instructor, Neuroimmunology division, Department of Neurology, UT Southwestern Medical Center

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INTRODUCTION

In 1868 Jean-Martin Charcot was the first physician to describe multiple sclerosis (MS). It wasn't until over a century later that the first treatment for MS, interferon beta, was introduced to the public. Since the early 1990's, over 20 therapies have received Federal Drug Administration (FDA) approval for MS, each carrying a unique risk profile. The current landscape of MS disease modifying therapy (DMT) can be daunting to the practicing neurologist, particularly given significant risks associated with higher efficacy options. This review provides an overview of recently approved DMTs for MS, and provides general guidance on their role in management.

SIPONIMOD

Siponimod (Mayzent) was FDA approved in March 2019 for relapsing remitting multiple sclerosis (RRMS), active secondary progressive disease multiple sclerosis (aSPMS), and clinically isolated syndrome (CIS). Siponimod shares it's mechanism of action with fingolimod (Gilenya), which was approved in 2010 as the first oral medication for MS. Siponimod is a selective sphingosine-1-phosphate (S1P) receptor modulator, which functions to reduce the egress of lymphocytes from lymphoid tissues.[1] This decreases the entrance of inflammatory lymphocytes into the central nervous system (CNS).[2] Centrally, Siponimod is thought to decrease S1P dependent processes, including hyperactivation and neurodegeneration.[2] Siponimod was FDA approved following the EXPAND trial, which found a 55% relative reduction in annualized relapse rate - an efficacy profile similar to fingolimod.[1]

Siponimod is an oral, once daily medication following an initial five day titration. Maintenance dosing of siponimod is 2 mg daily, with the exception of patients with a CYP2C9 *1/*3 or *2/*3 genotype, which requires a dosage adjustment.

Screening labwork should include complete blood count (CBC) with differential, liver function tests (LFTs), varicella zoster virus (VZV) antibody status, CYP2C9 genotyping, and urine pregnancy test in females. Patients without VZV IgG antibodies should undergo vaccination prior to commencing treatment. An EKG should be obtained to evaluate for conduction abnormalities; if present, cardiology evaluation prior to drug start is recommended. Similar to fingolimod, patients require first dose monitoring due to potential bradycardia. The patient should also have a fundoscopic exam. Special consideration should be given to patients taking antineoplastic, immunosuppressive, or immune-modulating therapies as there may be unintended additive immunosuppressive effects.

After initiation of siponimod, it is the practice of this author to obtain CBC and LFTs every three months during the first year of therapy, then every six months thereafter with ophthalmologic exams annually.

Patient's receiving siponimod should be monitored closely for infection, as circulating peripheral lymphocyte counts will be decreased by 20-30% of baseline.[3] Although the overall risk of infection is comparable to placebo, herpes virus infections, respiratory tract infections, and fungal skin infections were more common in individuals treated with siponimod than placebo.[3] Physicians should be vigilant in monitoring for cryptococcal meningitis, which has occurred in S1P receptor modulators. Progressive multifocal leukoencephalopathy (PML) is rare in individuals on monotherapy with S1P modulators, though risk is increased in those on multiple immunosuppressive agents.[3] Other potential side effects include headaches, macular edema, bradycardia, posterior reversible encephalopathy syndrome (PRES), atrioventricular conduction blocks, transaminitis, decreased lung function, and hypertension.

Siponimod should not be discontinued abruptly due to rebound disease activity potential. Immunomodulatory effects can last up to one month after drug discontinuation, therefore caution is advised with use of other immunosuppressants within this period.[3]

Siponimod should not be prescribed to patients who have a CYP2C9*3/*3 genotype, Mobitz type II second or third-degree AV block, sick sinus syndrome, or history of myocardial infarction, unstable angina, stroke, TIA, or decompensated heart failure within the past six months.

Role in therapy

Siponimod is an appropriate first line therapy choice for moderately aggressive disease in CIS and RRMS. It should also be considered for aSPMS cases, an advantage in labeling over fingolimod. Siponimod should be avoided in patients with a history of non-compliance given risk of rebound disease with drug discontinuation, as well as patients with history of uveitis or diabetes.

DIROXIMEL FUMARATE

Diroximel fumarate (Vumerity©) was approved by the FDA in October 2019 for CIS, RRMS and aSPMS. This is the second fumarate medication FDA approved for MS; the first, dimethyl fumarate (Tecfid-

← BACK TO PAGE 1 NEXT PAGE →

era©), was approved for RRMS in 2013. Monomethyl fumarate, the active metabolite of both therapies, activates nuclear (erythroid-derived 2) related factor mediated antioxidative response pathways.[4] This is thought to shift subset populations of B and T lymphocytes to an anti-inflammatory state.[4,5] Due to its distinct chemical structure, diroximel fumarate offers the advantage of improved gastrointestinal tolerability over dimethyl fumarate. This was evidenced in the EVOLVE-MS-2 study, which found after a five week head-to-head comparison that patients taking diroximel fumarate had a statistically significant reduction in symptom intensity scores, drug discontinuations, and gastrointestinal adverse events than those treated with dimethyl fumarate.[5]

Diroximel fumarate is an oral medication dosed twice per day; there is a one week titration period before maintenance dosing of 462 mg twice per day is achieved.

Similar to dimethyl fumarate, a CBC with differential and LFTs should be checked prior to initiation of diroximel fumarate. Thereafter, a CBC with differential should be collected every three months for the first year, then every six months for the duration of therapy. Due to a higher risk of developing PML, drug discontinuation should be considered for prolonged lymphopenia.

Flushing is a common side effect of fumarate medications, occurring in nearly half of patients. Administration of 325 mg of non-enteric coated aspirin 30 minutes prior to dosing may reduce the incidence and severity of flushing.[7] Additional side effects include transaminitis and lymphopenia, though there was no increase in infection rates compared to placebo in clinical trials.[7] Cases of PML have been reported in patients treated with dimethyl fumarate, typically in association with prolonged lymphopenia; to date, no cases have been reported with diroximel fumarate. As these drugs share a common mechanism of action, physicians should remain vigilant while monitoring for signs and symptoms of PML.

Role in therapy

Diroximel fumarate should be strongly considered in patients well controlled on dimethyl fumarate who are intolerant of the gastrointestinal side effects. It can also be considered as a first line therapy for low to moderately aggressive disease in CIS and RRMS.

CLADRIBINE

Cladribine (Mavenclad) was FDA approved in March 2019 for RRMS and aSPMS. Cladribine was originally FDA approved in 1993 under the proprietary name, Leustatin, as an intravenous therapy for active hairy cell leukemia. The mechanism of action in MS is not fully understood, but thought to be related to cladribine's activity as a purine antimetabolite, thereby impairing DNA synthesis and depleting B and T lymphocytes.[8] Cladribine's efficacy was demonstrated in the CLARITY study, which showed a reduced annualized relapse rate and lowered risk of disability progression in individuals treated with cladribine compared to placebo.[9]

Cladribine is an oral medication dosed over two treatment courses (each of which contain two treatment cycles) spaced one year apart. Each treatment cycle consists of a once daily medication for five consecutive days. Treatment cycles within a treatment course are spaced 23-27 days apart.

Screening studies include CBC with differential, LFTs, HIV, tuberculosis screening, Hepatitis B and C screening, VZV antibody status, and urine pregnancy test in females. The ALC should be within normal limits prior to the first treatment course and greater than 800 cells per microliter prior to the second treatment course.[10] Patients should be up to date on vaccinations based on standard recommendations; all live or live attenuated vaccinations should occur no less than four weeks prior to cladribine start. If patients are not immune to VZV, they should undergo vaccination prior to commencing treatment. Patients should be referred for all age and gender appropriate cancer screenings prior to starting cladribine.

Interval monitoring includes a CBC with differential at months two and six following each treatment course; if the ALC is below 200 at month two, begin monthly CBC monitoring until month six. If the ALC remains below 200 by month six, do not redose cladribine. MRI Brain should additionally be obtained within three months of drug start due to risk of PML.

Cladribine carries a black box warning for potential increased risk of malignancy and risk of teratogenicity. Patients should be counseled on effective contraceptive use during cladribine administration and for six months following administration. Lymphopenia occurs with nadir at two to three months following treatment; there is a corresponding increased risk of infections, especially herpes zoster and oral herpes.[10] Anti-herpes prophylaxis should be initiated for an ALC less than 200. Additional side effects include pancytopenia, hepatotoxicity, and transfusion related graft-versus-host disease. While there have been no cases of cladribine associated PML in MS patients, post marketing studies of patients treated with cladribine for oncologic indications have cited cases of PML.[10]

Cladribine is not recommended for individuals with CIS. Cladribine should not be prescribed to individuals with current malignancy, active infections, HIV, or who do not plan to use effective contraception during and six months following cladribine administration.

Role in therapy

Cladribine is a highly efficacious medication with minimal dosing requirements. However, due to the safety profile, cladribine should be considered as a second line agent in RRMS and aSPMS for moderate to severe disease.

OZANIMOD

Ozanimod (Zeposia) was FDA approved in March 2020 for CIS, RRMS and aSPMS. Similar to siponimod and fingolimod, ozanimod functions as an S1P receptor modulator sequestering lymphocytes in the peripheral lymphoid tissues.11 Due to the selective nature of receptor subset modulation in ozanimod, first dose monitoring is not required - a distinct advantage over other S1P receptor modulators.[12] Ozanimod does not require genetic testing prior to initiation, differentiating it from

← BACK TO PAGE 1 NEXT PAGE →

siponimod. Ozanimod's screening and monitoring studies are otherwise identical to siponimod. Ozanimod's approval was based on the clinical trials SUNBEAM and RADIANCE, head-to-head comparator trials against interferon beta-1a.[12] Ozanimod is a once daily oral medication achieving maintenance dosing after a seven day titration period.

Due to decreased circulating lymphocyte counts, patients are at increased risk of infections, particular viral upper respiratory tract infections (URTI), urinary tract infections (UTI), and herpes zoster. [12] The overall rate of infection was similar to interferon beta-1a in clinical trials.[12] Risk of serious infections such as cryptococcal meningitis and PML is similar to other S1P inhibitors.[3,12] Additional side effects include macular edema, bradycardia, transaminitis, decreased lung function, PRES, and hypertension. Rebound disease activity has been reported with abrupt discontinuation of ozanimod.[12]

Ozanimod should not be prescribed to individuals with severe untreated sleep apnea or those taking monoamine oxidase inhibitors. Cardiovascular contraindications to prescribing are identical to siponimod.

Role in therapy

Ozanimod is an appropriate first line therapy choice for moderately aggressive disease in CIS, RRMS, and aSPMS. It offers the advantage of increased S1P receptor modulator selectivity, therefore eliminating the need for first dose monitoring and genetic testing. Ozanimod should be avoided in patients with a history of non-compliance given risk of rebound disease with drug discontinuation.

OFATUMUMAB

Ofatumumab (Kesimpta©) was FDA approved in August 2020 for CIS, RRMS and aSPMS as a once monthly subcutaneous injection. This biologic was previously approved in 2009 as an infusion for chronic lymphocytic leukemia (CLL). Ofatumumab is an anti-CD20 monoclonal antibody resulting in B-cell depletion, similar to the infusion therapies rituximab and ocrelizumab.[13] It was approved following the ASCLEPIOS trials, which found ofatumumab increased the probability of achieving no evidence of disease activity when compared head-to-head with teriflunomide.[14] Ofatumumab is initially dosed at 20 mg via subcutaneous injection at weeks zero, one, and two, followed by one 20 mg monthly injection starting at week four.

Screening studies include Hepatitis B virus status and quantitative serum immunoglobulins. Patients should be up to date on vaccinations based on standard recommendations; all live or live attenuated vaccinations should occur no less than four weeks prior to ofatumumab start.[13] Common side effects include injection site reactions and headache.[13] An increased risk of infections has been seen in other B-cell depleting therapies; URTI and UTI were the most commonly identified infections in ofatumumab treated patients in clinical trials.[14] Hepatitis B virus reactivation leading to hepatic failure and death has occurred in patients being treated with ofatumumab for CLL, therefore ofatumumab should not be prescribed to individuals with active Hepatitis B infection.[13] Similarly, PML has occurred in patients being treated with ofatumumab for CLL, as well as patients treated with anti-CD20 antibodies for MS.[13]

Role in therapy

Ofatumumab is an appropriate first line or escalation therapy for CIS, RRMS and aSPMS in individuals with moderate to severe disease. It provides an alternative B-cell depleting therapy without necessitating the time and coordination required by patients for infusions.

FUTURE DIRECTIONS

The outlook for MS care remains optimistic with many promising therapies on the horizon. Notable mentions include remyelination therapies aimed at the reversal of prior damage and stem cell transplants acting as an immune system reset. DISCO-MS will additionally provide guidance regarding timing of treatment discontinuation as early as 2022.

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← BACK TO PAGE 1
NEXT PAGE →


Briana F. Syed


Meeta W. Cardon


Lindsay E. Elton

Improving co-prescription of antiepileptic medications and folic acid in women of childbearing potential seeking care at a Child Neurology practice to potentially reduce fetal malformations

Briana F. Syed[1], Meeta W. Cardon[2,3], and Lindsay E. Elton[2,3]

[1]*College of Natural Sciences and McCombs School of Business, The University of Texas at Austin*
[2]*Child Neurology Consultants of Austin*
[3]*Affiliate Faculty, The University of Texas at Austin- Dell Medical School*

INTRODUCTION

Folic acid supplementation among women of childbearing potential can help prevent 150,000-210,000 of the greater than 300,000 neural tube defects that occur yearly in low- and middle-resource countries[1]. Moreover, supplementation is considered especially important in women of childbearing potential with epilepsy taking antiepileptic drugs (AEDs), as AEDs are suspected to increase the risk of teratogenicity and major congenital malformations (MCMs) by greater than 50 percent[2]. One study showed the incidence of MCMs in women with epilepsy taking AEDs is 6.1%, compared to 2.8% in those with epilepsy not taking AEDs, and 2.1% in women without epilepsy who are not taking AEDs[3]. More recent studies have cast implications of negative impacts on intellectual disability as well, suggesting that children exposed to AEDs prenatally possess significantly lower IQ scores compared to their non-AED exposed counterparts[4].

In 2009, the American Association of Neurology (AAN) and the American Epilepsy Society (AES) reassessed the evidence available for the care of WWE surrounding pregnancy, and investigated the question of whether periconceptional folic acid supplementation reduces the risk of MCMs in the offspring of WWE taking AEDs. The authors concluded that, although data are insufficient to show definitive efficacy, there is no evidence of harm, and periconceptional folate supplementation may be an indicator of improved fetal development and decreased incidence of MCMs in WWE taking AEDs.

The goal of our quality improvement project is to 1) assess the rate of folate co-prescription with AEDs in women of childbearing potential regardless of underlying diagnosis and 2) increase this rate via various methods including an educational seminar and electronic reminders in a pediatric neurology outpatient clinic.

METHODS

As part of the initial screen, AthenaNet electronic medical records for Child Neurology Consultants of Austin were filtered to include all female sex patients between the ages of 12 and 65 years who had ICD10 diagnosis codes associated (in alphabetical order) with Anxiety Disorder, Bipolar Disorder, Disorder of the Brain, Disturbance of Skin Sensation, Dysthymic disorder, Dystonia, Epilepsy, Headaches, Major Depressive Diorder, Manic Disorder, Movement Disorder, Mood Disorder, Neurofibromatosis, Pain, Seizures, and Tic Disorder. The list was further filtered by those who had an AED prescription written from February 1, 2020 through February 29, 2020 and actively followed with one of the 5 physicians and one nurse practitioner who participated. The active prescriptions were any--brand, generic, and extended release--from this list: Clobazam, Ethosuximide, Lamotrigine, Levetiracetam, Oxcarbazepine, Phenytoin, Topiramate, Valproic Acid, and Zonisamide. The authors independently reviewed the charts to determine if clinical documentation indicated a recommendation for folic acid supplementation--regardless of dose--or if the medication list included folate at the time of the signed prescription for an AED in the indicated period in February 2020. The charts were then re-assigned to another author for an independent evaluation. Discordance was settled by the group of authors as a whole. IBM SPSS data analysis software was utilized to compute the initial pre-intervention co-prescription rate.

An educational seminar was implemented to inform the participating physicians and nurse practitioner of a large, single-specialty, private practice, primarily outpatient group--Child Neurology Consultants of Austin--of the evidence behind the practice guidelines set forth by the AAN and AES. This was conducted during a lunch conference from 12:15pm - 1pm CST via Zoom during the Coronavirus-19 pandemic. The need to document the physicians' recommendations for folic acid supplementation in the EMR and increase the rate of co-prescription of folic acid with AEDs was highlighted. Following this seminar, follow-up reminder emails were sent to all providers in the office every one to two weeks.

A final chart review was conducted 2 months after the conclusion of the seminar to calculate co-prescription rates for the 4- to 8-week posteducational seminar time interval and compare to the initial chart review co-prescription rate. Identical parameters in the AthenaNet medical records system were used with the dates changed to October 16, 2020-November 16, 2020. IBM SPSS data analysis software was utilized to compute Chi-squared and Fisher's Exact tests to evaluate the significance of the association between the preintervention and postintervention time periods and the outcome variable of folate co-prescription with AEDs, respectively. Given that data collection occurred as a part of a provider quality improvement intervention project, IRB approval was not necessary.

RESULTS

As part of the chart review for the period between February 1st - February 29th, 2020, a total of 140 patient charts from AthenaNet electronic medical records were collected. Of those 140, sixteen

← BACK TO PAGE 1 NEXT PAGE →

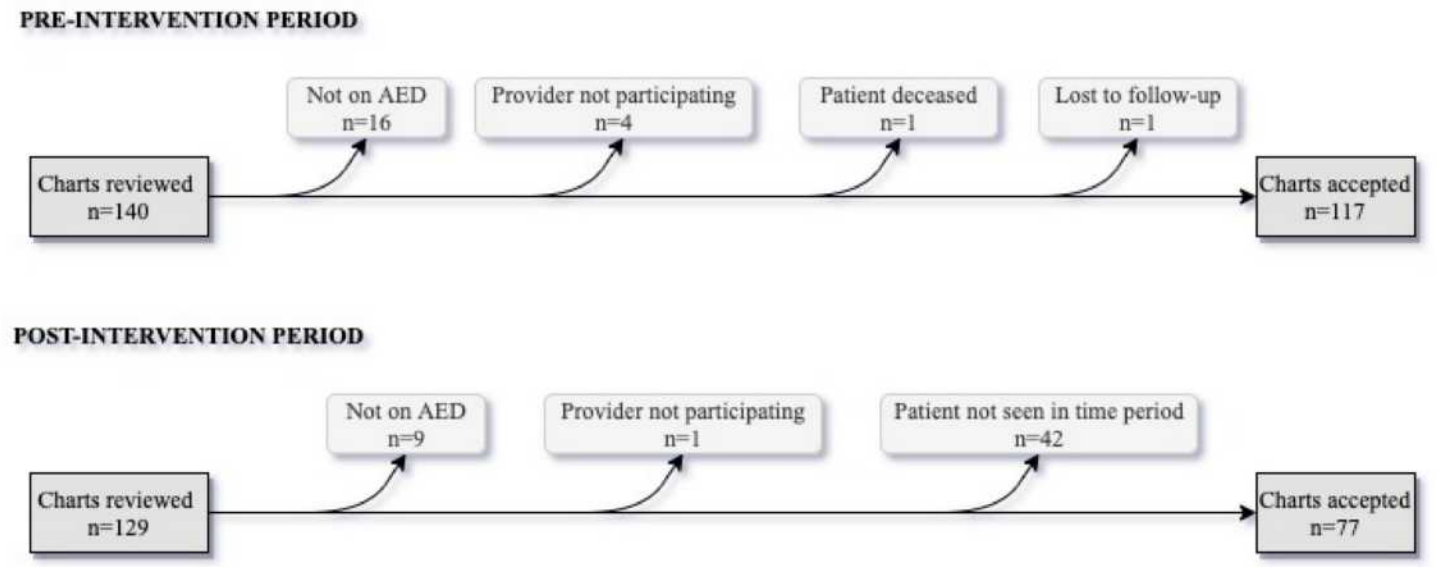

Figure 1. Flowchart demonstrating chart selection

patients were identified as not being on an AED at the time of the appointment, 4 patients were not primarily cared for by one of the providers that attended the educational seminar, 1 patient died, and 1 was lost to follow-up. Of the remaining 118 patients, eight were either recommended to take or prescribed folate at the time of their appointment, indicating an initial co-prescription rate of 6.8% for AEDs and folate.

Table 1

	PRE-INTERVENTION (N=118)	POST-INTERVENTION (N=77)
AGE RANGE	12-28 years	12-38 years
RECOMMENDED FOLATE	8 (6.8%)	14 (18.2%)
NON-EPILEPSY DIAGNOSIS	24 (20.3%)	20 (26.0%)

Table 1: Pre-intervention and post-intervention findings: Age ranges, folate recommendation rates, and non-epilepsy diagnoses. Recommendations to supplement with folate in adolescent females prescribed AEDs increased after an educational seminar and email reminders. Many patients were prescribed AEDs for non-epilepsy diagnoses.

In the second chart review for the period between October 16th - November 16th, 2020, conducted exactly 4-8 weeks following the educational seminar , a total of 129 patient charts were collected from AthenaNet utilizing the same filters. The charts were then independently reviewed in a procedure parallel to that used in February, and 9 patients were identified as not being on an AED at the time of appointment, 42 patient encounters were not in the form of a direct in-person or telehealth appointment (i.e. prescription refill orders or single-inquiry phone calls), and 1 patient was not followed by any of the participating providers. Of the 77 patients remaining, fourteen patients were either recommended to take or prescribed folate at the time of their appointment, indicating an improved co-prescription rate of 18.2% for AED and folate. Pearson Chi-squared and Fisher's Exact test indicate a significant association between the intervention time point relative to sample analysis and the incidence of the outcome variable of folate and AED co-prescription (P=.014).

Interestingly, 20.3% (24 of 118 patients) in the pre-intervention group and 26% (20 of 77 patients) in the post-intervention group were prescribed AEDs for purposes other than the treatment of epilepsy.

DISCUSSION

The results of the statistical analyses indicate that the implementation of an educational seminar had statistically significant positive effects on improving the rate of recommendation of folate to women of childbearing potential prescribed AEDsin the pediatric setting. This quality improvement intervention, in addition to a similar study conducted by Sharma, et al. in 2015, demonstrates not only the need for improvement in adhering to the practice guidelines set forth by the AAN and AES, but also the potential value in simple educational interventions to affect change in clinical practice. Despite such findings, the rate of folate supplementation in women of childbearing potential in general remains critically low--40%--and the rate of co-prescription of folate and AEDs is even lower, at less than 25% in one study of general Adult Neurology practice[5]. To our knowledge, this is the first evaluation of a Child Neurology practice as it encounters young females transitioning into a group with childbearing potential.

The role of periconceptional and gestational folate supplementation in neurodevelopmental outcomes has been previously studied. With an average of 7-point higher IQs in AED-exposed epilepsy patients taking periconceptional folate compared to AED-exposed epilepsy patients not taking folate, there is reason to believe that folate plays a role in improved neurodevelopmental outcomes[4]. This has been supported by Husebye et al., 2018, a study reporting that periconceptional folic acid supplementation during pregnancy was associated with fewer autistic traits in AED-exposed children[6]. In this cohort, 24% of AED-exposed children displayed significant expressive language delay compared to 6% in the control group of non-AED exposed children of mothers without epilepsy ($P < .001$), and 17% of AED-exposed children had significant global language delay at 18 months in comparison to 11% in the control group ($P = .01$). Interestingly, however, the same significance is not reflected between AED-unexposed children of mothers with epilepsy and the control group of nonepileptic mothers, indicating that the incidence of intellectual and developmental disorders (IDDs) is likely attributed to the

← BACK TO PAGE 1
NEXT PAGE →

concomitant diagnosis of epilepsy and AED usage--not an epilepsy diagnosis alone. With the potential to improve fetal health outcomes for women of childbearing potential, interventions to improve the co-prescription of folate with AEDs are especially important in clinical practice settings where AEDs are prescribed regularly to patient populations with epilepsy and other neurologic diagnoses.

For the group we evaluated, the folate co-prescription rate was remarkably lower than what was published from another center in Ohio within the past decade[5]. Some reasons for this could be age difference in patient population, differences in scope of practice, regional practice differences, larger group size, specific diagnoses differences (epilepsy vs non-epilepsy), and existing gaps in literature advocating for focused efforts to affect change in folate fortification for adolescent females. Although efforts are currently focused on adults, these habits are best established at a young age, and a woman does not have to meet legal criteria recognizing adulthood before exposing a fetus to an AED.

This study conducts a novel analysis of the reality of folate supplementation in a pediatric setting. Currently, existing literature addresses the need for adult maternal folate fortification to improve fetal outcomes, but does not highlight the need for the same folate supplementation in the pediatric population of women of childbearing potential. In the pediatric setting, pregnancy is not a well-defined or conventional area of concern when prescribing AEDs, but is a critical area of concern to improve fetal outcomes. The results of this study have shown that, in comparison to an adult practice setting such as that studied in Sharma et al. (2015), pediatric practice settings may face steeper shortfalls in folate and AED co-prescription. On the other hand, Pooya (2015) counters against the safety of folate supplementation, citing the potential significant drug–drug interactions between high doses of folic acid and some AEDs in patients with epilepsy as well as emerging evidence from animal studies that high levels of folic acid throughout gestation may have adverse effects on fetal brain development[7]. It becomes clear that the role of folate in improving fetal outcomes in the pediatric population is an active area of debate and necessitates further investigation.

The AAN and AES clinical practice guidelines released in 2009 included recommending at least 0.4 mg folate to all WWE from puberty to menopause. Such guidelines are likely to have implications beyond women with epilepsy. With greater than 50% of current AED prescriptions being targeted for pain and psychiatric disorders[8], AEDs are currently among the most common teratogenic drugs prescribed to women of childbearing age.

The precise dosage of folate remains ill-defined in the literature. One literature review revealed a range of 0.4 mg to 5 mg[9]. There is an ongoing need for the standardization of folate supplementation dosage, which may be affected by factors such as sex, age, pregnancy status, current medications, and genetic profile. In fact, a study by Nambisan et. al. (2003) concluded that maternal periconceptional folate use had no effect on the incidence of MCMs, but noted that folate dosage was not considered in their analysis, and a higher dosage could potentially reverse their findings[10].

CONCLUSIONS

The co-prescription of folate with AEDs has not been thoroughly investigated in pediatric neurology in spite of the potential to significantly impact clinical outcomes. Folate supplementation is currently recommended for all women of childbearing potential who are prescribed AEDs to reduce the risk of major congenital malformations; this recommendation includes the understudied pediatric population. In this study, the implementation of an educational seminar and intermittent email reminders improved the rates of folate co-prescription in one pediatric neurology practice. Based on the significant differences in MCM incidence between those with epilepsy taking versus not taking AEDs, there is a heightened need for further investigation of the plausible role of AEDs in fetal development as well as exploration of countermeasures effectively reducing such effects. AEDs are prescribed for many diagnoses beyond epilepsy, and physicians should be cognizant of both the potential impact on fetal outcomes as well as the need for co-prescription with folate. The rate of prescription of folate remains overall low, and we have yet to understand the link between AEDs, folate, and major congenital malformations; the specific dose at which folate is beneficial; and the specific factors influencing folate prescription in pediatric neurology clinical practice.

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← BACK TO PAGE 1
NEXT PAGE →

A prescription for exercise for people with epilepsy

Katherine M. J. Harris, MD

Assistant Professor of Neurology, Epilepsy
Fellowship Associate Program Director
McGovern Medical School, UTHealth – Houston

PHYSICAL ACTIVITY IN PEOPLE WITH EPILEPSY (PWE) – WHERE ARE WE NOW?

PWE often have sedentary lifestyles and a higher prevalence of obesity than the general population (Hinnell et al., 2010). Historically, there has been a cautious and even overprotective mindset toward PWE by their loved ones, caregivers, and healthcare professionals that adversely influenced the levels of physical activity (PA) in this population (Bjørholt et al., 1990). One of the guiding tenants in medicine emphasized in the Hippocratic Oath to "first, do no harm," from the Latin phrase, "primum non nocere," has doubtlessly contributed to past recommendations for PWE to avoid PA. In 1968, the American Medical Association (AMA) recommended restriction of contact sports for PWE to avoid injury or the possibility of inducing seizures (AMA Committee on the Medical Aspects of Sports, 1968). By 1974, the AMA position was modified to allow PWE to participate in contact sports with the caveat that "each participant should be judged on an individual basis" (Corbitt et al., 1974). Over the last few decades, there has continued to be a shift towards encouraging PWE to pursue PA and sports (Pimentel et al., 2015). In 2016, the International League Against Epilepsy (ILAE) published a report from the ILAE Task Force on Sports and Epilepsy that advocated for the participation of PWE in sports in the context of an individualized risk assessment (Capovilla et al., 2016). Despite this change, there have been multiple recent reviews concluding that PWE remain less active than their peers (Carrizosa-Moog et al., 2018; Johnson et al., 2020; van den Bogard et al., 2020; Vancampfort et al., 2019).

SAFETY AND BENEFITS OF PHYSICAL ACTIVITY IN PWE

PWE and their families often limit their PA because of safety concerns such as fear of injury if a seizure were to occur during PA or concern that seizure frequency may increase as a result of exercise (Pimentel et al., 2015). These apprehensions are largely unfounded. Though there have been reports of seizures induced by PA in PWE (Schmitt et al., 1994), this appears to be the exception rather than the rule. In a study of 400 PWE by Arida et al., only two participants had seizures induced by exercise (2009). Moreover, in 2016, the ILAE published a risk stratification of sports for PWE, including a group of sports that carries no significant additional risk of injury for PWE or bystanders (Capovilla et al., 2016). Additionally, there have been reports of physical activity reducing both seizure frequency and interictal epileptiform discharges in PWE (de Lima et al., 2011; Vancini et al., 2010) and even proposals that exercise should be included as a complimentary treatment for epilepsy (Arida et al., 2013).

PA can have many positive effects, including improved mood and sleep (Hartescu et al., 2015). It has been shown to improve depression in PWE and is also associated with a higher quality of life and improved cognition (Roth et al., 1994; Tedrus et al., 2017; Feter et al., 2020). The incidence of mood disorders in PWE is higher than the general population (Josephson et al., 2017). The prevalence of comorbid anxiety and depression in PWE was found to be 20.2% and 22.9%, respectively, in one recent meta-analysis (Scott et al., 2017). Armed with this knowledge, we need to do more for PWE by encouraging physical activity and educating our patients on how to exercise safely. Prescribing exercise could certainly serve as a low-cost treatment option to address multiple challenges faced by this population.

METHODS FOR INCREASING PHYSICAL ACTIVITY IN PWE – WHAT ACTUALLY WORKS?

The most commonly tested method of increasing PA in PWE has been required regular PA over an intervention period (Bjørholt et al., 1990; Eom et al., 2014; McAuley et al., 2001; Nakken et al., 1990). Although each of these studies reported positive outcomes, any physician can attest to the challenges of convincing patients to start a structured exercise program. Other studied methods have included behavioral counseling (Brown et al., 2019), exercise education and goal-setting (Dustin, 2019), and even epilepsy surgery (Leite et al., 2009). However, none of these approaches affected PA levels. In today's technological world, the natural next question is how we can apply existing technology to make PA more enticing to PWE in a way that could be feasibly incorporated into a busy physician's daily practice. Wearable physical activity trackers have been shown to increase physical activity in patients with chronic lung disease and heart disease and may be an effective tool to encourage increased physical activity in PWE (Alharbi et al., 2017; Qui et al., 2018). Thanks to a generous grant from the Texas Neurological Society in 2020, we were able to launch a randomized controlled clinical trial to further investigate the utility of activity trackers in PWE at UTHealth-Houston. Study enrollment is ongoing with 35 out of 80 planned participants currently enrolled at the time of this article's submission. Preliminary results will be presented at the upcoming Texas Neurological Society Winter Conference. The study protocol is included below.

Utilizing activity trackers to promote physical activity in people with epilepsy: can we make a difference?

Study Sponsor: Texas Neurological Society Research Grant - 2020

Principal Investigator: Katherine M. J. Harris, MD

Co-Investigators: Omotola A. Hope, MD, MHS; Alison Massie, DrPH; Morgan Talbot, BSN, RN; Kristofer Harris, MPH, BSN, RN; Lauren Skalomenos, MD; An K. Tran, DO; Joanna Wu, MD

Specific aim: The objective of this study is to evaluate stan-

← BACK TO PAGE 1 NEXT PAGE →

dard of care exercise education alone or in combination with a wearable physical activity tracker in PWE to determine the most effective way to increase physical activity and measure impact on depression, anxiety, quality of life, sleep, and seizure frequency.

Study design: This is an open parallel group prospective randomized trial. Participants will be adult PWE who see a physician affiliated with the Texas Comprehensive Epilepsy Program at UTHealth-McGovern Medical School. In order to enroll in the study, participants must have a diagnosis of epilepsy, be between 18 and 64 years of age, be able to provide consent in English, complete surveys independently, and sync Fitbit data. They also must not currently use a wearable physical activity tracker prior to enrollment, not currently be pregnant or planning to become pregnant during the study duration, and not be planning to undergo epilepsy surgery during the study duration. Participants will be randomized to either receive standard of care exercise education for PWE or to receive a Fitbit wearable activity tracker in conjunction with standard of care exercise education. There will be 40 participants in each group. The sample size is a convenience sample based on the number of activity trackers provided by grant funding. Primary outcome measures will be participant reported exercise frequency and duration. Participants in the activity tracker group will also have their daily step count, daily distance, and daily active minutes monitored. Secondary outcome measures will include depression, anxiety, quality of life, and sleep as measured by the Patient Health Questionnaire depression scale (PHQ-9), General Anxiety Disorder 7-item scale (GAD-7), Patient Weighted Quality of Life in Epilepsy (QOLIE-10-P), and Epworth Sleepiness Scale (ESS), respectively. Participants in the activity tracker group will be provided a Fitbit physical activity tracker. They will be asked to download the Fitbit application (app) to their personal smartphone device to allow them to see their own data collected by the Fitbit. They will also be asked to download the Stridekick app for the purpose of sharing their activity tracker data electronically with the study team and having the opportunity to participate in fitness challenges through the app. App accounts will be created by the participants with usernames that do not contain the participant's identifiable personal information. Optional fitness challenges will be created once per month by the study investigators, and participants will also receive a weekly message of encouragement from the study team. All participants will be asked to complete the PHQ-9, GAD-7, ESS, and QOLIE-10-P surveys at the time of study enrollment and at study completion. In addition to the questionnaires listed above, variables to be assessed and abstracted will include history of epilepsy diagnosis and etiology if known, age, sex, race, height, weight, medical comorbidities, exercise frequency and duration, preferred exercise type, seizure frequency/severity, seizure medications, medication changes, and other self-reported life changes. These variables will be collected at the time of study enrollment and tracked throughout the study approximately once per month via electronic RedCAP survey. Data will be collected from each participant continuously for 3 months with weekly review by the study team. If participants report an adverse change in seizure frequency, their epileptologist will be notified by the study team. Determination regarding whether the participant should continue with the study or withdraw from the study will be made jointly between the participant, their epileptologist, and the study team. Data will be logged in a password protected REDCap file. A separate linking log will contain patient identifiers (name, DOB, MRN). Each participant will be assigned a code to link his/her data to identifiers for data quality assessments. These will be stored in the secure REDCap database and accessible only to the Principal Investigator and Co-Investigators via password protection. Statistical analyses will be performed on the data collected.

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Aaron Desai

A new protocol for administration of Hypertonic Saline: A Quality Improvement Project

Aaron Desai[1], Muhammad Qasim[1], Asim Naveed[1], Ivan Cuesta Isabel[1], Khwaja Siddiqui[1], Muhammad Ubaid Hafeez[1], Muhammad Fahim[2], Mary-Claire Harris[3], Mohammad Hirzallah[1], Eric Bershad[1], Chethan Venkatasubba Rao[1], Rahul Damani[1]

[1]Section of Neurosciences Critical Care, Dept. of Neurology, Baylor College of Medicine.
[2]Dept of Pharmacy, CHI St. Lukes Woodlands Hospital.
[3]Dept of Pharmacy, CHI Baylor St Lukes Medical Center.

INTRODUCTION

Hyperosmolar therapy is a cornerstone for the management of elevated intracranial pressure (ICP) in patients with devastating neurological diseases. It has been used for almost two centuries, without clear understanding of underlying mechanism [1]. The first clear account of its mechanism of action came from the experiments of Lewis Weed and Paul McKibben in 1919 who discovered that intravenous administration of 30% hypertonic saline resulted in collapse of the lumbar cistern and profound decrease in brain volume and CSF pressure, whereas intravenous injection of water resulted in significant brain swelling in cats[2, 3]. Since then numerous agents such urea, glycerol, dimethyl sulfoxide (DMSO), mannitol and hypertonic saline have been used for the management of refractory intracranial hypertension and cerebral edema [4, 5]. Currently mannitol and hypertonic saline (HTS) are only two agents used for treatment of intracranial hypertension and cerebral edema.

A matter of frequent debate is the optimal dosing and administering strategy of hypertonic saline to achieve hyperosmolar effect by hypernatremia. Multiple studies have used either bolus dosing or continuous infusion[6, 7] of hypertonic saline for treatment of cerebral edema, however, head to head comparison studies are sparse .[8] . Recent guidelines from Neurocritical Care society concluded that there is no clear evidence of superiority of one over other [9]. The panel further suggested that there is a significant gap in the literature regarding the value of targeting a specific serum sodium concentration in patients with cerebral edema, and whether targeting specific serum sodium concentration is efficacious. Due to knowledge gaps regarding the administration of hypertonic saline, we devised a quality improvement project with pre and post design for a new protocol for administration of HTS in our neurosciences critical care unit (NCCU)t . We devised the protocol with the rationale that faster rate of administering hypertonic saline will lead to osmotic gradient which in turn will lower intracranial pressure (ICP) in patients with cerebral edema[10]. We aimed to establish safety and efficacy of faster rates of infusion.

METHODS

CHI St. Luke's Health- Baylor St. Luke's Medical Center is a large tertiary care hospital in Houston, Texas which is also a comprehensive stroke center. Our NCCU admits over 300 patients with cerebrovascular diseases like acute ischemic stroke, intracerebral hemorrhage and subarachnoid hemorrhage. Based on the high volume of patients, we sought to test our protocol for administering hypertonic saline in the

← BACK TO PAGE 1

NEXT PAGE →

Table 1.			
Baseline Values before starting hypertonic saline			
	Old Protocol- Mean (SD)	New Protocol- Mean (SD)	p-value
Sodium	139.27 (4.15)	141.57 (2.76)	0.17
Chloride	107.27 (5.51)	108.14 (4.91)	0.69
BUN	24.59 (19.25)	19.71 (10.78)	0.52
Creatinine	1.83 (2.36)	1.12 (0.63)	0.44
Values after reaching goal			
Sodium	147.05 (3.08)	148.71 (1.6)	0.17
Chloride	114.73 (20.49)	116.33 (6.15)	0.84
BUN	26.22 (21.0)	24 (16.06)	0.79
Creatinine	1.79 (2.14)	1.25 (0.99)	0.52

NCCU. The "Hypertonic Saline for Raised ICP & Cerebral Edema" protocol was developed jointly with the NCCU chief and staff; and the NCCU pharmacists through an iterative process based on the best evidence from the literature, our previous experience, and the previous protocol for the administration of hypertonic saline. The protocol was devised for different hypernatremia goals as follows:

Sodium goal 145-150
Initiate sodium acetate 3% at 50 mL/hr via centra/peripheral line and titrate accordingly to the sliding scale below to a targeted Na level 145 - 150 mEq/L.
If Na level is less than 130 mEq/L, increase rate by 15 mL/hr (max rate of 80 mL/hr).
If Na level is 130 - 135 mEq/L, increase rate by 10 mL/hr (max rate of 80 mL/hr).
If Na level is 136 - 140 mEq/L, increase rate by 5 mL/hr (max rate of 80 mL/hr).
If Na level is 141 - 144 mEq/L, increase rate by 5 mL/hr (max rate of 80 mL/hr).
If Na is at ordered target, continue current rate of infusion.
*If Na is greater than 150 mEq/L at any time, HOLD infusion for 1 hour, reduce the current rate by 10 mL/hr, and call physician.

Sodium Goal: 150-155
Initiate sodium acetate 3% at 50 mL/hr via centra/peripheral line and titrate accordingly to the sliding scale below to a targeted Na level 150 - 155 mEq/L.
If Na level is less than 135 mEq/L, increase rate by 20 mL/hr (max rate of 80 mL/hr).
If Na level is 136 - 140 mEq/L, increase rate by 15 mL/hr (max rate of 80 mL/hr).
If Na level is 141 - 145 mEq/L, increase rate by 10 mL/hr (max rate of 80 mL/hr).
If Na level is 146 - 150 mEq/L, increase rate by 5 mL/hr (max rate of 80 mL/hr).
If Na is at ordered target, continue current rate of infusion.
*If Na is greater than 155 mEq/L at any time, HOLD infusion for 1 hour, reduce the current rate by 10 mL/hr, and call physician.

Pre (old protocol) data was retrospectively collected from January 2018 to December 2019, while post (new protocol) data was prospectively collected from January 2020 to November 2020. Baseline demographics and along with following variables were collected, history of end stage renal disease, type of solution (sodium chloride or sodium acetate), reason for administration, goal sodium, reason for stopping infusion, baseline sodium level, maximum sodium level, baseline chloride level, maximum chloride level, baseline blood urea nitrogen (BUN) level, maximum BUN level, baseline creatinine level, maximum creatinine level, time to achieve target sodium level (hours). Data are reported using standard descriptive statistics. Statistical analysis for each outcome variable was performed with IBM SPSS v27 software. Analysis of variables was performed using Chi-square test for categorical data and a two tailed t-test for continuous data. For all statistical analyses, $p<0.05$ was consid-

Table 2.			
	Old Protocol- Mean (SD)	New Protocol- Mean (SD)	p-value
Sodium Max	155.81 (5.21)	158.71 (5.59)	0.23
Chloride Max	124.08 (6.13)	124.29 (7.8)	0.95
BUN Max	34.68 (23.34)	36.29 (17.63)	0.86
Creatinine Max	1.99 (2.54)	1.29 (.91)	0.47

← BACK TO PAGE 1 NEXT PAGE →

ered statistically significant. Based on our institutions policy, our study being a quality improvement initiative, qualified for Institution Board Review (IRB) waiver.

RESULTS

A total of 44 patients were included in the analysis, 37 patients (mean age 63, 49% female) received infusion per the old protocol and 7 (mean age 55, 86% female) patients received infusion per the new protocol. The indication for infusion of hypertonic saline was cerebral edema secondary to either subarachnoid hemorrhage, acute ischemic stroke or intracerebral hemorrhage. The mean sodium, chloride, BUN and creatinine levels before starting the hypertonic saline and on reaching goal are shown in table 1 for both groups. The mean time to achieve goal sodium was 22.96 hours (standard deviation 19.51) for the old protocol group and 13.81 hours (standard deviation 8.12) (p-value =0.23). The mean maximum sodium, chloride, BUN and creatinine levels for the old protocol vs the new protocol group are shown in table 2. In terms of complications, one patient developed left arm phlebitis secondary to infusion of 3% sodium chloride via a peripherally inserted central catheter in the old protocol group. There were no side effects related to infusion in the new protocol group. A careful analysis of the data revealed that 13 patients in the old protocol group were transitioned from 3% sodium chloride to 3% sodium acetate which is associated with lower events of hyperchloremia and acute renal insufficiency. All 7 patients in the new protocol group were started on 3% sodium acetate group which may account for the similar events of hyperchloremia and acute renal insufficiency across both groups.

DISCUSSION

Our results indicate that the new protocol developed to achieve a faster sodium goal is effective in reaching goal sodium levels, without increased risk of developing hyperchloremia and acute renal insufficiency compared to old protocol. This study has various limitations. Our significant limitation was related to the slow enrollment of the patients and small sample size. Due to COVID-19 pandemic, Neuro critical care units across the country were utilized for the care of those patients leading to lower admission rates for acute neurological emergencies like acute ischemic stroke, subarachnoid hemorrhage and intracerebral hemorrhage[11-13]. Similarly, our neurocritical care was transitioned to care for those affected with COVID-19 leading to lower admission rates. The other limitation of this study, partly being retrospective in nature, might be its inherent susceptibility to unrecognized confounding factors. One such factor is the infusion of 0.9% normal saline in patients prior to starting 3% hypertonic saline. However, we did record baseline sodium levels in patients just before starting hypertonic saline which might help offset its effects.

CONCLUSION

Our new protocol for administration for hypertonic saline showed a shorter time to achieve goal sodium levels in patients with cerebral edema and raised intracranial pressure, however, it didn't reach the level of significance due to small sample size.

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← BACK TO PAGE 1 NEXT PAGE →

Development of a Comprehensive Epileptic Spasms Program in a Tertiary Care Center

Danielle S. Takacs, MD

Assistant Professor, Department of Pediatrics and Neurology, Neurophysiology and Epilepsy, Baylor College of Medicine/Texas Children's Hospital

Epileptic spasms represent the most common form of infantile epilepsy and is associated with significant morbidity in the pediatric population, often with devastating consequences for a child's development and intellectual function. It is thought that this diagnosis is made in approximately 2-3 per 10,000 children1, and at the largest Children's Hospital in the U.S., this diagnosis is encountered on nearly a weekly basis. Despite its frequent presentation, there have been difficulties in standardizing the care and follow up of these patients, in part due to controversies in the history of its treatment, but also in the need for frequent and timely follow up visits, EEG evaluation, and changes to the treatment regimen to ensure response to treatment of choice. Furthermore, it is believed that earlier initiation of treatment is more effective in controlling spasms and improving outcomes. 2,3,4

Through the support of our institution administrators and a generous grant from the Texas Neurologic Society, we have been able to establish a comprehensive treatment program for the identification, management, follow up, and coordination of care for patients and families with Epileptic Spasms (ES), used synonymously with Infantile Spasms (IS). In doing this, we have created a patient registry, which will be used for data collection, and guidance of evidence-based management protocols in the future. The need for such a program was identified through observing several areas in need of improvement:

- Timely and accurate diagnosis.
- Appropriate and standardized treatment initiation.
- Prompt outpatient follow up and subsequent objective EEG data to assess treatment response.

We sought to focus on these main objectives in our initial formation of the Spasms Program. The program is currently in its infancy, with the official Spasms clinic having started in September 2020, however, the initial steps of this process began in early 2020. We first developed standardized procedures for accurate diagnosis of ES and provided education regarding the urgency of identification and prompt treatment for best outcomes. Often, the initial diagnosis of epileptic spasms is delayed due to the subtle clinical nature of early spasms. This may not be recognized as an ominous sign by parents, pediatricians, or even some neurologists. Furthermore, even with appropriate clinical concern, a routine EEG is often inadequate to capture spasms and/or hypsarrythmia, and thus a prolonged study is ideal.

To assist in early diagnosis, we created and distributed a standardized algorithm outlining the approach to the identification and treatment of ES. Once a diagnosis of spasms and/or hypsarrhythmia is confirmed, we then also provided a standardized treatment algorithm based on the most updated evidence available (Figure 1). Protocols were distributed throughout the neurology department and at our affiliated community hospitals. Standardized workup included hospital admission with overnight prolonged EEG monitoring, imaging, laboratory workup for treatable metabolic/genetic conditions. We held a "Spasms Educational Series" of lectures – including several educational briefings discussing the "Basics and Treatment of Spasms," "EEG characteristics of Spasms," and "Diagnostic Workup of Spasms Etiology", as well as a specific session focusing on the logistics of how to successfully order and schedule studies needed in our hospital system, including the 2 week follow up overnight EEG, and step-by-step instructions on how to order specialty medications. Given that our center is an academic institution, we recognized that frequent review of these processes was necessary. Therefore, a monthly "refresher" session is held with the inpatient primary neurology team trainees each month to ensure that new rotators on the service are familiar with the process of epileptic spasm management. Future directions include educational seminars for general pediatric practitioners, discussing the importance of early recognition and urgent referral for evaluation of epileptic spasms.

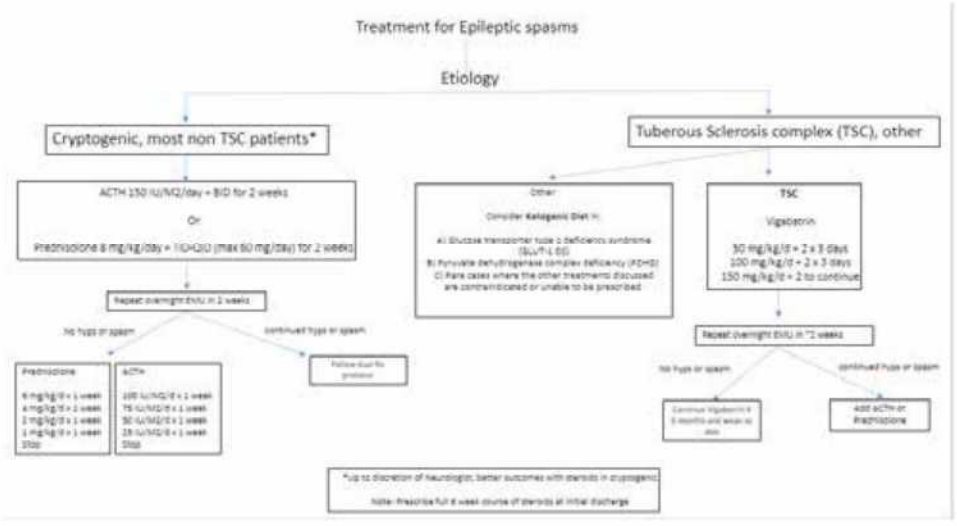

Fig. 1. Institutional Treatment protocol for Epileptic Spasms. Abbreviations: Hypsarrythmia (hyps), Tuberous Sclerosis Complex (TSC)

← BACK TO PAGE 1 NEXT PAGE →

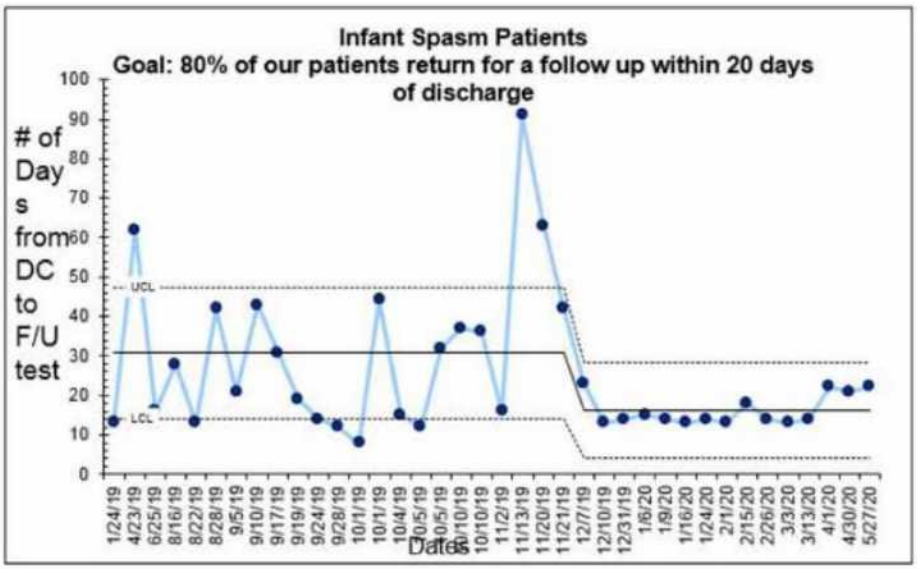

Fig. 2. Significant improvement in follow up extended EEG occurred after implementation of a standardized workflow and educational sessions in early 2020. Abbreviations: Discharge (DC); Follow Up (F/U)

While inpatient, the patient is placed the patient on appropriate therapy: hormonal therapy (high dose prednisone at 8 mg/kg/day or ACTH 150 IU/m2/day) or vigabatrin titrated to 150 mg/kg/day (used in Tuberous Sclerosis patients or those with contraindication to hormonal therapies).4,5,6 However, we noted prior to the program establishment that there were frequent errors in medication prescriptions or lack of appropriate weaning instructions given. Given that ACTH and vigabatrin are specialty medications, the correct prescription process is vital to the timely and appropriate initiation. Furthermore, there are known and potentially severe side effects to these medications, and therefore prompt establishment of an outpatient provider is crucial. The successful implementation of treatment would not be possible without the involvement of our program nurse coordinator and our nursing administrator – which have been an invaluable line of communication. These team members have been instrumental in reducing the errors in prescriptions especially at our teaching institution. Trainees and neurology faculty now have specific contact persons to consistently reach out for assistance in completing specialty medication forms, and reduction in any errors. Additionally, the nurse administrator and nurse coordinator establish communication with the families to establish outpatient follow up, and address concerns promptly as they arise. We have seen a significant reduction in instances such as delays in medication initiation and patient follow up. With the program, families now have a prompt outpatient follow up visit scheduled 1 week after hospital discharge, which has aided in monitoring clinical response to treatment, as well as discussing possible clinical outcomes and prepares the family next steps in treatment options. This establishment of an outpatient provider has been important, especially given that there have been several patients who developed hypertension in response to being on hormonal therapies. To best address these concerns, multidisciplinary meetings were held with renal and endocrine colleagues to discuss appropriate monitoring and treatment of such side effects as hypertension or hyperglycemia.

Another aspect of this project that has become evident is the importance of the objective data that the 2 week follow up EEG provides in order to assess response to initial medications. Due to the subtle clinical nature of these epileptic events, parents often underestimate the number or presence of ES, however studies with objective data and EEG confirmation are lacking.7,8,9 Unfortunately, due to institutional limitations or lack of protocols, many centers are unable to perform prolonged monitoring for follow up characterization of treatment response. Routine EEGs often miss the diagnosis of ES and/or hypsarrythmia, which may only be present during sleep. For these reasons, extended EEG monitoring is recommended to evaluate response to treatment, especially at 2 week follow up. A practice improvement committee was formed in order to identify barriers to this process, and we met our goal of having at least 80% of our newly diagnosed and spasms patients with a follow up overnight EEG in the EMU within 14-20 days of diagnosis and treatment, as seen in Figure 2.

This two week interval monitoring data was also instrumental in assessing trends in parental reporting of spasm response to treatment. In the first year of observing this trend, we compiled data on 28 patients with new onset ES, evaluating response to 14 days of appropriate medical therapy, and comparing parental report of ES with the extended overnight EEG monitoring study results. We were happy to note that of the 28 patients identified the majority (71%) of patients were initiated on proper treatment within 24 hours of diagnosis. Exceptions (initiation ranging from 2-10 days) were attributed to insurance issues or prescription errors. Prolonged video EEG within 14-18 days of starting appropriate therapy was performed. Overall accuracy of parental reporting was 64% (18/28). Out of these, 50% (9/18) reported resolution of ES and 50% (9/18) reported continued ES. Of the 36% (10/28) families who were incorrect at the 2 week follow up, 70% (7/10) reported resolution of ES. However, a significant minority of families, 30% (3/10), who continued to report spasms clinically, were inaccurate. (Table 1)

While a majority of these patients were inaccurate due to unrecognized spasms (a widely known and documented phenomenon), 7,8 a significant minority were conversely inaccurate due to persistent over-reporting of spasms. Many epilepsy centers may not perform follow up EEG study after two weeks of

← BACK TO PAGE 1 NEXT PAGE →

Initial EEG with Hyps? (Y/N)	Report Spasms continue	Report Spasms Resolved	Is parent Accurate?	f/u EEG w/ spasms?	Hyps on f/u EEG?	Symptomatic (S) vs Cryptogenic & subcategory
Y		X	Y	N	N	S-structural
N		X	Y	N	N	S- structural
Y	X		Y	Y	N	S- genetic
Y		X	Y	N	N	S - structural
N		X	Y	N	N	S - structural
Y	X	X	Y	Y	N	S - genetic
Y	X		Y	Y	N	S – structural
N	X		Y	Y	N	S - structural
Y		X	Y	N	N	S - structural
N	X		Y	Y	N	S – structural
Y	X		Y	Y	N	S - structural + genetic
Y		X	Y	N	N	Cryptogenic
Y		X	Y	N	N	S – genetic
N		X	Y	N	N	S - genetic
N		X	Y	N	N	S- structural +genetic
N		X	Y	N	N	S- structural + genetic
Y	X		Y	Y	N	S- genetic
N	X		Y	Y	N	S- structural
Y		X	N	Y	N	S- structural + genetic
N	X		N	N	N	Cryptogenic
Y		X	N	Y	N	S- genetic
Y		X	N	Y	N	S- genetic + structural
Y		X	N	Y	N	Cryptogenic
Y	X		N	N	N	Cryptogenic
Y		X	N	Y	Y	Cryptogenic
N		X	N	Y	N	S- structural + genetic
Y	X		N	N	Y	S - structural
Y		x	N	Y	N	S - structural
18 of 28 + Hyps			10 of 28 inaccurate	15 of 28 with continued spasms	2 of 28 with continued Hyps	5 of 28 cryptogenic etiology
67.86%			35.71 %	53.57%	7.14%	17.86%

Table 1. Characteristics of patients with new onset epileptic spasms (ES) identified on EEG, and parental reporting of response after 2 week follow up. Abbreviations: Electroecephalopgram (EEG), Hyps (hypsarrythmia). Genetic conditions identified included Trisomy 21, variants in STXBP1, CDKL5, KANSL1, TSC2, genes, and Timothy Syndrome.

treatment if families continue to report spasms. However, in such cases, if formal monitoring is not performed, then inappropriate escalation of medication therapy may increase the risk significant adverse effects and unnecessary healthcare costs. Therefore, we conclude that ideally a follow up overnight video EEG at the two week mark should be done to assess response to treatment, even if families continue to report spasms.

These are just a few examples of the insights we have gathered in our evaluation of these patients. However there is much more to be learned from this cohort of patients with newly diagnosed epileptic spasms. This project will continue with the goal of generating continued improvements in the recognition and management of this condition, and the expansion of an ES registry and comprehensive treatment program will then allow for further study of treatment efficacy and long-term developmental outcomes seen in this condition. We are currently working with our institution's Evidence Based Outcomes Committee in order to widely publish our protocols across institutional websites. We hope (particularly after the limitations of COVID-19 pandemic are eased), to provide and implement further educational materials to medical professionals in primary care in order to improve the early identification and treatment this condition in a standardized fashion. Additionally, future programs will be aimed at education and support for families, public health awareness activities, and informational seminars.

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← BACK TO PAGE 1 NEXT PAGE →

Aziz Shaibani, MD

Refractory Chronic Immune-Mediated Demyelinating Polyneuropathy

Aziz Shaibani, MD, Director, Nerve and Muscle Center of Texas, Houston, Texas, Clinical Professor of Medicine, Baylor College of Medicine

Husam Al Sultani, MD, Nerve and Muscle Center of Texas, Houston, Texas

INTRODUCTION

Chronic immune-mediated demyelinating polyneuropathy (CIDP) is the most common treatable neuropathy. It is an autoimmune disorder of the peripheral nerves which, on average, affects 5:100.000 of the population [1]. There are no universally accepted diagnostic criteria. 50% of those diagnosed by community practitioners and 18% of those enrolled in clinical trials based on expert's diagnosis, received different diagnoses after further evaluation [2]. There are more than 15 sets of diagnostic criteria that vary in specificity and sensitivity, leaving a room for misdiagnosis, particularly in the absence of accurate diagnostic biological markers [3]. We prefer the European Federation of Neurological Societies and the Peripheral Nerve Society (EFNS/PNS) criteria for this purpose [4].

Only 50% of patients meet the diagnostic criteria of typical CIDP. These diagnostic problems together may explain part of the fact that 20% of patients are refractory to first-line treatments (steroids, gammaglobulins and/or plasmapheresis) [5]. Approximately, half of these patients received an alternative diagnosis with further evaluation.

The most common causes of treatment failure are:

- Inadequate immunosuppression.
- Alternative diagnoses [6] including amyotrophic lateral sclerosis, small fiber neuropathy, Charcot Marie Tooth disease, Inclusion body myositis, amyloid neuropathy, diabetic polyneuropathy, POEMS and Anti MAG neuropathy [2].

CIDP variants like multifocal motor neuropathy and NF-155 antibodies syndrome require more aggressive therapy. Some classical cases of CIDP are associated with a more aggressive and refractory immune attack. Usually, these are associated with axonal damage.

Common sources of misdiagnosis are:

- A liberal interpretation of electrodiagnostic findings.
- Reliance on mild cytoalbuminemic dissociation (In most real CIDP cases, the CSF protein level is >100 mg/dL, and elevations as high as 10 times the upper limits of normal are occasionally seen).
- Putting too much emphasis on patient's reported outcome measures [2].

While a review of the diagnostic criteria is beyond the scope of this chapter, a review of the cardinal feature of CIDP is important.

The cardinal features of CIDP are:

- Slowly progressive course over more than 8 weeks of the proximal and distal weakness of the upper and lower extremities.
- Large fiber more than small fiber loss (ataxia is more pronounced than pain or dysautonomia).
- Motor more than sensory symptoms.
- Diffuse areflexia.
- Demyelinating findings in nerve conduction study.
- Elevated cerebrospinal fluid protein.

Cardinal neurophysiological findings are:

- Prolonged distal motor latencies.
- Delayed f-responses.
- Motor slowing.
- Conduction block.
- Temporal dispersion. Distal temporal dispersion seems to be the most specific of the demyelinating features [6].

Nerve biopsy usually shows:

- Segmental and paranodal demyelination.
- Inflammation is seen in less than 15% of cases.

Usually, nerve biopsy is unnecessary for most patients with suspected CIDP, especially those with typical electroclinical findings. Nevertheless,
Nerve biopsy is used mainly:

- When other studies fail to establish the diagnosis of CIDP clearly.
- When electrophysiologic criteria for demyelination are not met.
- There is high suspicion for an infiltrative or vasculitis process [7].

This chapter will display several videos of real cases of refractory CIDP referred to a tertiary neuromuscular clinic. Each case will be discussed and some light will be shed on the basis of the diagnosis and misdiagnosis.

CASE 1

(See video 1: https://1drv.ms/v/s!AuM2slBEjNxNijQ27LaL-wRDqgMr6?e=CCggXB)

Case Presentation

- A 70 year- old woman presented with a one-year history of progressive feet and hands numbness.

← BACK TO PAGE 1 NEXT PAGE →

- Loss of balance due to sensory ataxia.
- Proximal legs and arms weakness.
- Elevated CSF protein (180 mg/dl).
- Frank peripheral nerves demyelination with multiple conduction blocks, temporal dispersions, prolonged distal latencies and delayed F responses in multiple nerves.
- She responded to IVIG for a year, then to PLEX.
- She relapsed several times but responded to an increasing frequency of IVIG and/or PLEX.
- The last relapse did not respond to IVIG, PLEX, and IVSM and she progressed to respiratory failure and passed away.

Clinical Questions
The most likely diagnosis is:

1- Severe CIDP
2- POEMS
3- GBS
4- NF-155 antibodies associated CIDP
5- DADSAM

Discussion

- The case illustrates the fact that some CIDP cases follow a progressive and none responsive course from the beginning or later on. There are no clear risk factors identified to justify or predict such a drastic course.
- A recent paper suggested the benefit of Bortezomib in these cases [8].
- It is important to note here that when treating a patient with CIDP, before considering IVIG as ineffective, a biweekly regiment is to be tried [6].
- Low compound muscle action potentials amplitudes and active denervation of the weak muscles by EMG suggest an axonal injury which is a bad prognostic factor.

CASE 2

Case Presentation

- A 76 YOM with 5 years history of poor balance and feet numbness
- Examination showed:
  - Mild weakness of the feet extensors (4/5 MRC). Normal proximal strength.
  - Proprioceptive loss in the feet
  - Absent DTR in the legs and arms
- CSF protein was 140 mg/dl
- NCS revealed:
  - Severe prolongation of the DMS and DSL and normal F waves
  - Mild motor slowing. No CB or temporal dispersion.
- A 3 months course of IVIG was ineffective.

Clinical Questions
The most likely positive test is:

1- Elevated VEGF serum level.
2- Elevated NF-155 antibody titer.
3- Elevated urinary lead level.
4- Elevated MAG antibody titer and IgM spikes.
5- Elevated GM1 antibody titer.

Discussion
MAG antibody-associated NP (Distal acquired demyelinating sensory and motor neuropathy; DADSAM)

- A demyelinating neuropathy with IgM monoclonal gammopathy (usually IgM Kappa). It is the most common paraproteinemic neuropathy.
- 50%-70% of cases have MAG antibodies. These antibodies are considered pathogenic because IgM and complement are deposited on the myelin sheath, splitting the myelin lamellae, while the adoptive transfer of patients' IgM into susceptible host animals causes sensory ataxia and reproduces the human pathology [9].
- Predominantly distal weakness (foot extensor weakness) and large fiber sensory loss (ataxia) are characteristic features.
- NCS shows severe prolongation of DML and DSL with no major slowing or proximal demyelinating features.
- Responds poorly to treatment with IVIG and an immunosuppressive agent. Two clinical trials of rituximab failed to show statistically significant improvement compared to placebo.
- It is important to investigate and monitor the level of the monoclonal protein. Waldenstrom macroglobulinemia may result from malignant transformation of the IgM monoclonal gammopathy.
- Otherwise, It may be safer to just monitor the patient clinically than to take the risk of immunomodulation.

CASE 3

(See video 2A: https://1drv.ms/v/s!AuM2slBEjNxNi-jqr-veCHTlw5XpS?e=WQccyc)

Case Presentation

- A 28-years-old female with the inability to get up from a chair and frequent falls, that evolved over days.
- Those were preceded a month earlier by acute feet numbness.
- Muscle pain, cramping, hoarseness, slurred speech, double vision, poor coordination, and fatigue were also reported.
- Past medical history revealed controlled Diabetes Mellitus, and gastric sleeve surgery a week before the symptoms started.
- CSF protein level was 479 mg/dL with no pleocytosis.
- NCS revealed severe prolongation of distal motor latencies, severe motor slowing, temporal dispersion and prolonged F responses in multiple nerves, and absent sensory responses in the limbs.

← BACK TO PAGE 1 NEXT PAGE →

- Brain MRI was normal.
- The patient was diagnosed with CIDP
- Unfortunately, she responded only slightly and transiently to IVIG and developed severe hemolytic anemia.
- Later, she mildly and transiently responded to a 5-day course of intravenous methylprednisolone, followed by a monthly booster for 3 months.
- Normal IFPE and VGEF level
- MAG antibodies were negative
- There was a noticeable improvement in function after plasmapheresis treatment as shown in the video (see video 2B: https://1drv.ms/v/s!AuM2slBEjNxNijXIb-7CGzd7h0NFN?e=Za3C8W).

CASE 4

(See video 3A: https://1drv.ms/v/s!AuM2slBEjNxNijeZnmId-WdF8-bL4?e=Br9PQO)

Case Presentation

- A 53 years-old male with a history of DM presented with progressive ataxia developed over weeks.
- Ascending numbness in the hands and feet
- A weakness of the handgrips and hip flexor weakness
- Lost 5 pounds
- Diffuse areflexia
- CSF protein was 420 mg/dl
- Normal Brain MRI
- Nerve conduction study is shown below (See table 1)

Nerve	Distal latency	amplitude	Conduction velocity
Left peroneal motor	11.34 msec	2.2 mv	33 m/sec
Left Tibial motor	11.39 msec	1.8 mv	27m/sec
Left median motor	10.3 msec	5.5 /2.2mv	21 m/sec
Left ulnar motor	7.47 msec	3.1 mv	34m/sec
Left sural nerve	3.55 msec	23mv	
Right sural nerve	3.58 msec	24mv	

Table 1: Nerve conduction study for case 4 showing Onset, amplitude and conduction velocity for multiple nerves of the upper and lower limbs. Credit: Shaibani, MD. Nerve and Muscle Center of Texas.

- There was a noticeable improvement in function after Rituximab treatment as shown in the video (see video 3B: https://1drv.ms/v/s!AuM2slBEjNxNijbfI6laUt-bq98iB?e=ejRzsU).

Clinical Questions

Regarding the above two cases, the following test will be most likely to be abnormal and diagnostically useful:

1- MAG antibody titer
2- NF-155 antibody titer
3- IgM level
4- VEGF
5- IgG level

Discussion

- The electrodiagnostic findings showed demyelinating motor neuropathy. The proximal median motor conduction block is very significant as this is not a conventional site for focal slowing.
- Neurofascin-155 IgG4 (NF155) antibody titer was elevated, confirming the diagnosis of NF-155 antibody-associated CIDP.

Features of NF-155 antibody-associated CIDP [10]

- NF-155 antibodies were recovered from 7% of 533 sera from CIDP patients.
- Earlier age of onset.
- Cerebellar signs are common. In this case, the ataxia is much more cerebellar than sensory.
- Severe peripheral demyelination.
- Very high CSF protein.
- CNS demyelination.
- Responds less frequently to IVIG.
- NF-155 is a member of the L1 family of adhesion molecules
- It is expressed at the paranodes by the terminal loops of myelin.
- It is associated with the axonal cell adhesion molecules CNTN1 and Contactin-associated protein-1 (Caspr1).
- Antibodies to NF155 block Neurofascin and inhibit interaction with CNTN1/Caspr1.
- Specifically, IgG4 binding to NF155 causes paranode dismantling and conduction defects, surprisingly without inflammatory cell infiltration.
- Patients with Neurofascin antibody-mediated CIDP have distinct pathological features compared to patients with typical CIDP:

- Lack of macrophage infiltrates
- Selective loss of the transverse bands at the paranodal loops
  - This kind of CIDP is strongly related to HLA-DRB1*15 which is reported in 10 of 13 patients with CIDP who were positive for anti-NF155 compared to only 5 of 35 patients with CIDP who were negative for anti-NF155

- Genetic studies showed that NF155 glycoprotein is encoded by NFASC. Inactivation of NFASC in adult mouse cerebellar Purkinje cells causes a rapid loss of NFASC glycoproteins, which might explain the predominant cerebellar signs and symptoms associated with anti-NF155-associated CIDP variant.
- Other causes of "refractory CIPD" such as multiple

← BACK TO PAGE 1 NEXT PAGE →

myeloma, POEMS syndrome, MAG antibody syndrome, and Castleman disease are not associated with cerebellar abnormalities.
- Take home message: check antibodies to NF-155 in refractory CIDP especially with cerebellar tremor
- The best therapeutic approach to this kind of CIDP is not known but there are case reports of good response to Rituximab or PLEX. The first patient responded to PLEX and the second patient responded to Rituximab.

CASE 5

(See video 4: https://1drv.ms/v/s!AuM2slBEjNxNijjsJthT_H2wcUNx)

Case Presentation
- A 55YOM with 4 months history of progressive distal numbness and proximal weakness
- With diffuse areflexia.
- CSF protein was 155 mg/ml
- The patient responded to IVSM and PLEX partially and temporarily
- He gradually needed more frequent treatments.
- He developed the changes shown in the following video: (See video 4)

Clinical Questions
The most likely abnormal and diagnostically useful test is:
1- VEGF
2- MAG antibody titer
3- NF-155 antibody titer
4- Serum IgM level
5- Serum Lead level

Discussion
- The video showed brownish discoloration and thickening of the skin of the hands and feet. The patient developed ascites and CT abdomen showed splenomegaly.
- Further testing revealed VEGF level of 486 (normal values: 31-86)
- Monoclonal gammopathy of IgA lambda type was also found.
- He used to report to the ER almost weekly for abdominal paracentesis and he stopped responding to PLEX.
- The patient made full recovery after auto-PBSCT (peripheral blood stem cell transplantation)

POEMS:
POEMS is a Paraneoplastic neuropathy associated with osteosclerotic myeloma and is characterized by:
- Peripheral neuropathy: the most prominent feature
- Organomegaly
- Endocrinopathy
- M protein (monoclonal gammopathy)
- Skin changes: hyperpigmentation, hypertrichosis, plethora, hemangiomata, white nails

Diagnostic criteria of POEMS
The diagnosis requires meeting both mandatory major criteria (neuropathy and monoclonal gammopathy), one major and one minor criterion. [11].
- Mandatory major criteria:
1- Polyneuropathy, typically demyelinating
2- Monoclonal plasma cell proliferative disorder
- Other major criteria:
3- Castleman disease
4- Sclerotic bone lesions
5- VEGF elevation
- Minor criteria:
  1- Organomegaly (hepatomegaly, splenomegaly, lymphadenopathy)
  2- Extravascular volume overload (ascites, edema, pleural effusion)
  3- Endocrinopathy
  4- Skin changes
  5- Papilledema
  6- Thrombocytopenia

Compared to CIDP, POEMS is characterized by:
- Affecting older patients with the average age being in mid 50s (CIDP affects patients in mid-40s)
- Shows Less cranial nerve involvement (2% vs 18%)
- More muscle atrophy.
- More distal weakness
- More pain (76% vs 7%): usually starts with feet pain
- More positive neuropathic sensory symptoms
- More uniform demyelination and axonal loss
- Does not respond to traditional therapy
- VEGF is increased. It is 68% sensitive and 95% specific
- Thrombocytosis occurs in 50% of cases (vs 2% in CIDP)
- auto-PBSCT is a very effective treatment [12].

CASE 6

(See video 5: https://1drv.ms/v/s!AuM2slBEjNxNij0-URgJyST-VLYE8?e=jagL2M)

Case Presentation
- She was referred because the insurance denied more IVIG despite the reported improvement by the patient.
- Nerve conduction study is shown below (see Table 2)

Site	Onset (msec)	Normal onset (msec)	OP amp (mv)	CV (m/sec)	Normal cv (m/sec)
Left peroneal motor	NR				
Right peroneal motor	NR				
Right median motor	9.09	<4.6	8.06	23.57	>50
Left median motor	8.36	<4.6	9.8	21.34	>50
Left ulnar motor	7.00	<3.6	8.13	23.37	>50

*Table 2: Nerve conduction study for **case 6** showing Onset, amplitude and conduction velocity for multiple nerves of the upper and lower limbs. **Credit**: Shaibani, MD. Nerve and Muscle Center of Texas.*

← BACK TO PAGE 1 NEXT PAGE →

Clinical Questions

The most appropriate next step is:

1- Nerve biopsy to look for demyelination/ inflammation
2- Testing for hereditary demyelinating neuropathy
3- Continue IVIG as findings are consistent with CIDP
4- Repeat EMG/NCS in 6 months
5- Test for serum MAG antibodies.

Discussion

- The NCS showed uniform severe demyelinating neuropathy. Temporal dispersion and CB are important for the diagnosis of CIDP. Acquired demyelinating neuropathy is mostly asymmetrical and patchy and the weakness is due to conduction block rather than due to demyelination. On the other hand, in hereditary demyelinating polyneuropathy, the failure of the formation of myelin is diffuse and does not cause severe weakness despite severe motor slowing.
- Objective measures are important to monitor outcome of therapy. Allen and Lewis studied 59 patients referred with the diagnosis of CIDP, 47% turned out to have a different diagnosis such as ALS, small fiber neuropathy, fibromyalgia, etc. When the outcome measure relied on patients reported subjected symptoms, 89% of CIDP and 85% of none CIDP patients reported improvement. Subjective improvement is caused by the placebo effect, the wish of the patient and physician to see improvement and by other none specific factors. Grip dynamometer and Rasch-built overall disability scale (r-ODS) are recommended to measure response to treatment and to avoid unnecessary prolonged and expensive courses of treatments that are not risk-free.
- Nerve biopsy is no longer indicated for the diagnosis of the hereditary or acquired demyelinating neuropathies.

CASE 7

(See video 6: https://1drv.ms/v/s!AuM2slBEjNxNijl_PV9B94lVPB-s?e=Ysgxpg)

Case Presentation

A 42-year-old female of a mixed African-American and Latin-American ancestry referred to Nerve and Muscle Center of Texas to confirm the diagnosis Miller-Fisher syndrome

- A non-ambulatory, cachectic, deaf woman
- Abdominal bloating, nausea and chronic diarrhea.
- Profound external ophthalmoplegia, and ptosis.
- Dysarthria
- Profound hypotonia, areflexia, muscle atrophy of the lower extremities
- Sensation was intact
- Fundoscopic exam – no pigmentary retinopathy
- NCS: demyelinating sensorimotor polyneuropathy
- MRI: enhancing lesions in the basal ganglia and diffuse white matter changes
- CSF studies
  - Protein: 101 mg/dl (15 to 45 mg/dL)
  - Resting serum Lactate: 4 mmol/L (1.1-2.2 mmol/L)
  - Resting serum Pyruvate: 2 mmol/L (0.04-0.1 mmol/L)
- Normal CPK

Clinical Questions

The most likely diagnosis is:

1- Miller Fisher Syndrome
2- GBS
3- CIDP
4- Mitochondrial demyelinating neuropathy
5- DADSAM

Discussion

- Muscle biopsy revealed many ragged red fibers and COX-negative SDH positive fibers highly suggestive of mitochondrial dysfunction. (see figure 1 and figure 2: https://1drv.ms/u/s!AuM2slBEjNxNij5JQf2ppX0JYrzG?e=1Q3O1T)
- Ptosis, ophthalmoplegia, gastrointestinal dysmotility, cachexia, demyelinating neuropathy, and leukoencephalopathy are symptoms of MNGIE (Mitochondrial Neuro-Gastro-Intestinal Encephalopathy)
- Onset is usually between the first and fifth decades; in about 60% of individuals, symptoms begin before age 20 years
- All cases of MNGIE are associated with demyelinating neuropathy [13]. The presence of multifocal manifestations especially encephalopathy, seizures, and deafness should raise the possibility of mitochondrial disease and lead to screening measurement of resting serum lactate and pyruvate. Muscle biopsy is rarely needed as the diagnosis can be easily made by genetic testing on WBC to study the nuclear mitochondrial genes. In other mitochondrial disorders which are due to mutations of the mitochondrial DNA itself, muscle tissue is more sensitive than white blood cells.
- Acute exacerbation of different clinical manifestations of MNGIE may be caused by infections or other sources of stress.
- Classic MNGIE is caused by thymidine phosphorylase (ECGF1) deficiency and is associated with increased plasma thymidine level. Pathogenic mutations of TYMP gene (nuclear gene) are typical. It is an autosomal recessive condition.
- RRM2B mutations are also reported to cause MNGIE [14]

CASE 8

(See video 7: https://1drv.ms/v/s!AuM2slBEjNxNijsw6xu8Rbo7_-26?e=laghkY)

Case Presentation

- The patient disclosed a history of MGUS

- The patient responded to IVIG for several years but his response decreased with time.
- He developed severe LBP.
- He developed anemia
- SPEF: M protein increased to 3 gm/dl over a year.

Clinical Questions
The most likely cause of refractory CIDP is :

1- POEMS
2- Multiple myeloma
3- MAG antibodies
4- NF-155 antibodies
5- Waldenstrom macroglobulinemia

Discussion

- This patient had typical CIDP for years, responding well to therapy then he progressed and became less responsive.
- This case illustrates the importance of serial measurement of IFPE in patients with MGUS to detect malignant transformation early which can cause loss of response to therapy.
- A skeletal survey revealed multiple osteolytic lesions in the skull. Bone marrow biopsy revealed increased clonal plasma cells to 60%. Treatment of the MM leads to remission of the CIDP.
- Monoclonal gammopathy of unknown significance (MGUS) occurs in 4% of individuals above age 50 years [15]. The rate of transformation of MGUS to malignant myeloma is 1% per year [16].
- MGUS requires the presence of:
  - Serum monoclonal protein (M-protein) at a concentration <3 g/dL
  - Bone marrow with <10 percent monoclonal plasma cells
  - Absence of end-organ damage (lytic bone lesions, anemia, hypercalcemia, renal insufficiency or hyperviscosity) related to the proliferative process.
- The appearance of anemia, hypercalcemia, bone pain and renal impairment in a patient with MGUS, should always raise the suspicion of malignant transformation.

CASE 9

Case Presentation

- A 66YOM with progressive painless pure motor weakness of the arms and legs proximally and distally.
- Absent DTR.
- Normal sensation
- Mild CSF protein elevation.
- Failed adequate IVIG therapy for three months.
- NCS: motor nerves were in 30s range and slightly prolonged distal latencies. Normal sural responses.
- EMG: widespread denervation including fasciculations.

Clinical Questions
The most likely diagnosis is:

1- CIDP
2- ALS
3- Amyloid neuropathy
4- POEMS
5- SMA

Discussion

- ALS may be confused as CIDP mostly due to the associated motor slowing and areflexia in the progressive muscular atrophy variant [17].
- Mild slowing of motor nerves is seen in motor neuron diseases due to the loss of large motor neurons which contribute to nerve conduction velocity.
- Diagnosis of CIDP should not rely on soft neurophysiological findings but on validated diagnostic criteria.
- Another source of mistake is the measurement of the distance of a MUAP from atrophies muscles. As figure 3 shows (see figure 3A and 3B: https://1drv.ms/u/s!AuM2slBEjNxNij-xhLPbri3_zc2w?e=Vbzyl5), when the gain was changed, the onset of the MUAP was earlier and the conduction velocity was closer to normal.

SUMMARY

- Causes of none responsiveness of CIDP
  - Wrong diagnosis
  - Severe disease with secondary axonal damage
  - Inadequate immunosuppression
  - Transformation to malignancy
- CIDP is rarely a straight forward diagnosis and different sets of diagnostic criteria have different sensitivities and specificities.
- Diagnosis should not be made based on soft findings in isolation such as mild elevation of CSF protein, mild demyelinating changes or subjective response to treatment.
- Failure to respond to first-line therapies should prompt revision of the diagnosis before subjecting the patient to more aggressive treatment.
- Some causes are not responsive to immunotherapy like CMT, ALS, and DADSAM.
- Others require more aggressive or specific therapies such as POEMS, MM and NF-155 associated CIDP (nodopathy).
- If not cause is found and the diagnosis is confirmed, more aggressive treatment with one or more modality including IVIG, IV steroids and PLEX would be warranted. Some patients require weekly or biweekly IVIG or PLEX. Rituximab and cyclophosphamide are used as a second line of therapy.
- Physical therapy is an important adjunct to immunomodulatory therapy.

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← BACK TO PAGE 1 NEXT PAGE →

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Clinical Trials with the Houston Nerve and Muscle Center – Aziz Shaibani, MD, principal investigator

Recruitment for Upcoming Clinical Trials

The center has been busy finalizing procedures for new needed clinical trials. I am pleased to inform you that we have started recruiting for the following clinical trials. To refer patients to the trials, please do not hesitate to leave a note via the website, and we will call the patient promptly. If you need to talk to me, feel free to call my cellular phone number at 713-906-0988 or leave a message at the Research Department phone at 713-654-4900.

2020-2024	A Randomized, Double-blind, Multicenter, Placebo-controlled Phase 3 Study With Open-label Period to Evaluate the Efficacy and Safety of Inebilizumab in Adults With Myasthenia Gravis
2020-2024	A Phase 3, Double-Blind, Randomized, Placebo-Controlled, Parallel Group, Multicenter Study With an Open-Label Extension to Evaluate the Efficacy and Safety of Ravulizumab in Patients With Amyotrophic Lateral Sclerosis (ALS)
2020-ongoing	An Adaptive, Phase 3, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study to Assess the Safety and Efficacy of Engensis in Participants With Painful Diabetic Peripheral Neuropathy.
2020-ongoing	A Phase 2, Randomzed, Double-Blind, Placebo-Controlled, Parallel-Group, Mulitcenter Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of LX9211 in the Treatment of Diabetic Peripheral Neuropathic Pain
2020-ongoing	A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study of Ricolinostat in Patients With Diabetic Neuropathic Pain
2020-ongoing	A Phase 3b, Multicenter, Randomized, Double-Blind Study to Evaluate Efficacy and Safety of Oral Edaravone Administered for a Period of 48 Weeks in Subjects With Amyotrophic Lateral Sclerosis (ALS).

← BACK TO PAGE 1 NEXT PAGE →