TEXAS NEUROLOGICAL SOCIETY SUMMER 2025

Broca's Area

The Voice of Texas Neurology

Katie Hendley, MD

President's Message

Dear Colleagues,

I'm excited to share that 2025 is off to a fantastic start for the Texas Neurological Society. Our collective momentum continues to grow as we strengthen our mission to support neurologists and promote excellence in neurological care across the state.

Our advocacy efforts are in full swing this legislative session. The Society remains actively engaged during the 89th Texas Legislature, working to ensure that the voice of Texas neurology is heard loud and clear. Our top priorities include the support of the Mobile Stroke Unit Grant Program designating $5 million appropriation to deploy additional mobile stroke units at hospitals across Texas. This will fund additional mobile stroke unit programs in Texas, especially benefiting patients in rural and underserved areas. Additionally, Mobile Stroke Unit Licensure (HB 4743/SB 2479), would allow hospitals to operate mobile stroke units under their existing hospital licenses. This would streamline the operations of mobile stroke units in Texas, enhance reimbursement for services, and promote a broader adoption of the MSU concept in communities across Texas. This emphasizes mobile stroke units' potential in improvingpatient outcomes and lowering long-term healthcare costs associated with stroke-related disability.

Dementia Prevention and Research Institute of Texas (DPRIT), is a $3 billion state-funded initiative to advance dementia research. TNS strongly supports this measure for its potential to transform neurologic research and improve public health across the state. If the Legislature approves, the proposal would ultimately go before Texas voters as a constitutional amendment to secure funding for DPRIT. From protecting patient access to care to supporting key reforms that impact our practice environment, your involvement and support make a meaningful difference.

Looking ahead, I'm thrilled to invite you to our TNS Summer Conference, taking place July 18-19 in San Antonio. This year's meeting promises dynamic programming, outstanding speakers, and plenty of opportunities to connect with colleagues from across the state. Whether you're a returning attendee or a first-timer, we hope you'll join us for what is sure to be an engaging and energizing event.

Thank you for your continued dedicated and for being an essential part of the TNS community. I look forward to seeing you in San Antonio!

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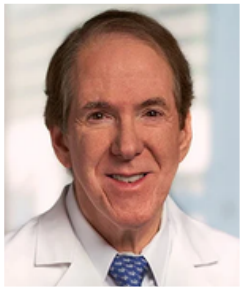

Editor's Notes

Randolph W. Evans, MD

THIS ISSUE

I thank our officers and other contributors for their excellent submissions to this issue. We look forward to seeing you at the TNS Summer Conference at the La Cantera in San Antonio, July 18-19. Program directors Jaya Trivedi and Irfan Sheikh; Erin Furr-Stimming, chair; and the education committee have planned an excellent program.

ACCURATE MEASUREMENT OF BLOOD PRESSURE (BP)

We're all familiar with the importance of hypertension as a risk factor for cerebrovascular, cardiovascular, and renal disease with a gradually increasing incidence of cardiovascular mortality as the blood pressure rises about 110/75. [1] Hypertension is the single most treatable risk factor for stroke.[2]

Over the years, I've been astounded by how often I witness improper measurement of BP both inpatient and outpatient which is typically relegated to medical assistants and hospital technicians. I have also been amazed as how few medical students and residents know how to take an accurate BP. It is also important for us to instruct our patients on proper home measurement of BP.

The position statement from the Lancet Commission on Hypertension group, "Optimizing observer performance of clinic blood pressure measurement"[3] is well worth reviewing. The overall global adult prevalence of hypertension is 31%. A 5mm Hg BP measurement error can lead to incorrect hypertension classification in 84 million people worldwide. Unstandardized BP measurement can alter management decisions in 20-45% of cases. Because of the constant change in BP due to endogenous factors and exogenous stimuli, it is more difficult than it may seem to obtain an accurate read of "usual" BP. "Multiple readings over time are required to estimate the usual BP, allow for regression to the mean, and reduce the white-coat effect."

The statement recommends automated BP measurement with a cuff that fits to reduce observer error. Choose an automated device from the US Blood Pressure Validated Device Listing.[4] Because there are questions about accuracy, brachial BP measurement is preferred over wrist measurement.[5] Wrist measurement may be necessary when you cannot obtain a large enough cuff or in patients who have had axillary lymph node resections. When measuring at the wrist, keep the wrist in the neutral position at heart level.

There are numerous sources of error during BP measurement.

Patient-related errors can arise from the following factors within the range of mean error in SBP and DBP as follows:
acute meal ingestion (-6/-5 to -2)
acute caffeine use (-3 to +14/+2 to +13)
acute nicotine use (+3 to +25/+3 to +18)
bladder distention (+4 to +33/+3 to +19)
white coat effect (up to +26/up to +21).

Procedure-related sources of error include the following with the range of mean error in SBP and DBP as follows:
Insufficient rest (+4 to +12/+2 to +4)
Legs crossed at knees (+3 to +15/+1 to +11)
Arms lower than heart (+4 to +23/+3 to +12)
Talking during measurement (+4 to +19/+5 to +14)
Fast deflation rate (-9 to -3/+2 to +6)

Equipment-related sources of error include the following with the range of mean error in SBP and DBP as follows:
Automated device variability (-4 to +17/-8 to +10)
Too small a cuff (+2 to +11/+2 to +7)
Too large a cuff (-4 to -1/-5 to -1)

Preparation before taking BP includes the following:

1. If possible, the patient should have an empty bladder and not have eaten or ingested caffeine, smoked or engaged in physical activity for at least 30 minutes.
2. The patient should be sitting comfortably in a quiet environment for 5 minutes in a chair with the back supported. During measurement, feet on the floor, and legs uncrossed.
3. The **entire** arm should be supported with the BP cuff at heart level (mid sternal) by the entire arm (arm and forearm) resting on a table or armrest at heart level or by the observer holding the entire arm at heart level. If the arm is extended and unsupported, the diastolic BP can be raised as much as 10%.
4. No talking during measurement by patient or observer.
5. The inflatable bladder width should be about 40% of arm circumference and bladder length should be about 80-100% of the person's arm circumference.
6. The lower edge of the cuff should be 2-3 cm above the elbow crease and the bladder should be centered over the brachial artery.

In a recent study of 133 adults, BP was measured in the following 3 positions: arm supported on a desk with midcuff approximately at midheart level; hand supported on the lap; and arm unsupported at the side.[6] Compared to the desk position, the following positions had significantly higher SBP and DBP readings as follow: lap (3.9/4) and side (6.5/4.4). When the arm is positioned at levels lower than the heart, there is an increase in hydrostatic pressure in the brachial artery, decreased venous return, and compensatory vasoconstriction. Muscle contraction in an unsupported arm can elevate BP.

Many diagrams don't clearly illustrate the following: "The forearm must also be at the level of the heart as denoted by the mid-sternal level."[7]

THE IQ

A recent NY Times article discussed speculation over Elon Musk's IQ.[8] One biographer estimated 100-110. An economics commentator estimated more than 130 based upon his SAT score. Others have speculated 155. The concept of IQ has been separated in the popular domain from the standardized testing with the Wechsler Adult Intelligence Scale (WAIS-IV/V). A brief refresher on the history of IQ testing may be of interest.

Sir Frances Galton. - Sir Francis Galton (1822-1811) was an English polymath and, unfortunately, also invented the term, eugenics, in 1883.[9] Among his many contributions, he devised the first weather map and presented evidence that each fingerprint is unique.

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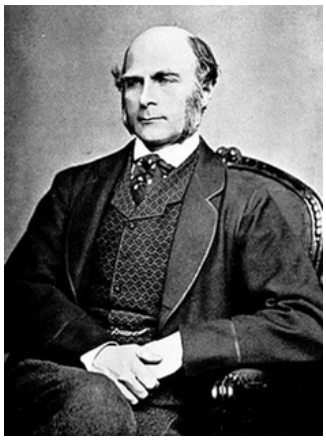
When he read "On the Origin of Species" (written by his cousin, Charles Darwin), he was convinced that nature and not nurture determined hereditary ability and decided to prove this. His 1886 publication popularized the concept of regression to the mean. He also pioneered the use of the questionnaire and invented the standard deviation. He was the first to apply statistical methods to the study of human differences and the inheritance of intelligence.



Galton in the 1850s or 1860s (from https://en.wikipedia.org/wiki/Francis_Galton)

Binet and Simon - In 1905, the French psychologist, Alfred Binet (1857-1911), and the French psychiatrist, Théodore Simon (1873-1961), began the development of the Binet-Simon intelligence test to predict academic performance in children.[10]

IQ. - The concept of the "Intelligence Quotient (IQ)" was introduced by German psychologist, William Stern (1871-1938), in 1912.[11] He proposed the following formula: IQ = mental age / chronological age x 100. If a child's mental age was the same as their chronological age, the IQ would be 100, "average" intelligence for that age group.

Terman. - The Stanford psychologist, William Terman (1877-1956), published the Stanford revision of the Binet-Simon Intelligence Test in 1916 with revisions in 1937 and 1960, initially as an aide for the classification of developmentally disabled children. [His son, Frederick Terman, and William Shockley were fathers of Silicon Valley.] Terman also used an average IQ score of 100. In 1917, Terman was a consultant to Robert Yerkes in developing the Army Alpha and Army Beta (for non-English speakers and the illiterate) tests administered to 1.75 million men by the US Army.

Wechsler. - David Wechsler (1896-1981), chief psychologist at Bellvue Psychiatric Hospital, first developed the Wechsler-Bellvue intelligence test in 1939 to measure intelligence (defined as "... the global capacity of a person to act purposefully, to think rationally, and to deal with his environment"[12]) of his patients. A revision, the Wechsler Adult Intelligence Test (WAIS) Form 1 was published in 1955.

David Wechsler conducting a test on a patient (From https://en.wikipedia.org/wiki/David_Wechsler)

WAIS-5. - The fifth edition (WAIS-5) was released in 2024 by Pearson using normative data collected in 2023-2024 from a US Census reflective sample.[13] The age range for the test is 16-90 years with a completion time of 60 minutes for the 10 primary index subtests and 45 minutes for the 7-subtest Full Scale (FSIQ). The WAIS-5 provides a FSIQ score which represents a person's overall general intellectual ability and scores on 5 primary index scales representing different cognitive domains (verbal comprehension index, visual spatial index, fluid reasoning index, working memory index, and processing speed index).

General intellectual ability as measured by the WAIS-5 is a significant predictor of educational attainment, occupational success, income, and health. However, there are numerous critiques. Holden and Tanenbaum argue that assessments of intelligence must be fair and equitable.[14]

Sternberg proposes that intelligence is not a fixed trait.[15] "Some might view "true" intelligence as manifesting itself only under quiet conditions with an airy, temperature-regulated room, and a decent desk at which to work, but intelligence in the real world occurs under many different kinds of circumstances. ...intelligence is in the interaction of person x task x situation, and there is no single number that will well capture how people will handle different ranges of situations. ...Of course, we all recognize that people who society labels, one way or another, as "intelligent" often act stupidly or foolishly. ...intelligence is more like creativity and wisdom."

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Advocacy Update

Kimberly Monday, MD, Legislative Affairs Chair and Tom Holloway, TNS Lead Lobbyist

The 89th Texas Legislature marked one of the most successful sessions in the history of the Texas Neurological Society. From transformative investments in dementia research to funding and licensing reforms aimed at expanding Mobile Stroke Units across the state, this session delivered landmark wins for Texas neurologists and the patients we serve.

Dementia Prevention & Research Institute of Texas (DPRIT)
SB 5 and SJR 3, authored by Sen. Joan Huffman (R-Houston) and Rep. Tom Craddick (R-Midland), establish the Dementia Prevention and Research Institute of Texas (DPRIT) – a $3 billion state-funded initiative to advance prevention, treatment, and research into Alzheimer's disease, Parkinson's, ALS, and other neurodegenerative conditions.

Modeled on the successful Cancer Prevention and Research Initiative, DPRIT aims to accelerate the development of therapies that can alter or delay disease progression and improve quality of life. From clinical trials and translational research to building a public health response to dementia, DPRIT will help position Texas as a national leader in neurologic research.

Both SB 5 and SJR 3 passed the Texas Legislature with overwhelming bipartisan support. Final approval of the $3 billion in funding to support DPRIT now rests with Texas voters, who will have a chance to vote on the issue in the November 2025 constitutional election. If voters approve the proposal, DPRIT could begin issuing grants as early as 2026.

TNS will continue to work with stakeholders, research institutions, and public health advocates to educate Texans about DPRIT and support its adoption by voters. This initiative represents the most significant state-level investment in brain health in U.S. history, and its passage is critical for the advancement of neurology in Texas.

Mobile Stroke Unit Licensure
For several sessions, TNS has worked within the legislature to raise awareness and support for the expanded utilization of mobile stroke units. This session, those efforts were finally rewarded.

HB 4743, filed by Rep. Greg Bonnen, MD, and sponsored by Sen. Donna Campbell, MD, allows mobile stroke units (MSUs) to operate under the license of a host hospital and provides a regulatory framework to support the expansion of this novel treatment method. Working under the license of a host hospital provides MSUs with greater long-term operational certainty, allowing them to utilize procedure codes and receive reimbursement for advanced services, such as CT imaging, which they currently cannot do.

By authorizing hospital-based licensing of Mobile Stroke Units (MSUs), HB 4743 establishes a means by hospitals and EMS providers to deploy mobile stroke units in a greater number of communities across Texas, providing neurologists with the opportunity to deliver faster and more effective treatment to stroke patients when every minute counts.

Dr. James C. Grotta MD – TNS member and pioneer of the Mobile Stroke Unit concept in the United States – testified before the House Public Health Committee, highlighting the importance of rapid stroke diagnosis and treatment, and how MSUs reduce time-to-treatment, improve patient outcomes, and decrease the long-term costs of stroke-related disability. Dr. Grotta's early work, which proved the efficacy of prehospital stroke treatment, has shaped national guidelines and saved lives. His leadership and vision in promoting the concept of mobile stroke care to both lawmakers and the Texas Neurological Society laid the foundation for HB 4737.

HB 4743 passed the House and Senate without opposition and has been sent to Governor Abbott for his signature. If signed, the bill will take effect on September 1, 2025.

$5 Million for Mobile Stroke Unit Grant Program
In another dramatic victory for stroke care access, the Texas Legislature included $5 million in grant funding for Mobile Stroke Units in the final version of the 2026-27 state budget. The appropriation will fund a competitive grant program to support the acquisition, deployment, and operation of mobile stroke units (MSUs) at hospitals across the state.

The Texas Neurological Society advocated for the funding throughout the legislative session, engaging both House and Senate budget writers and emphasizing the high-impact outcomes MSUs offer. For communities with limited access to stroke centers, MSUs represent a solution to reduce death and disability from stroke by bringing the emergency room to the patient.

The grant program will help hospitals, particularly those in underserved or rural areas, overcome the cost barriers to adopting this technology. With this funding secured, TNS will work closely with the Department of State Health Services to ensure effective implementation of the grant program, expanding MSU access to the patients and regions who need it most.

Expansion of Medical Cannabis
In one of the session's more unexpected developments, the 89th Texas Legislature enacted a host of transformative changes to the state's limited medical cannabis program, the Texas Compassionate Use Program (TCUP).

HB 46, authored by Rep. Ken King (R-Canadian), expands the list of qualifying conditions for medical cannabis to include chronic pain, traumatic brain injury, Crohn's disease, and terminal illnesses. This expansion is particularly significant for neurologists who treat patients suffering from conditions like neuropathic pain and neuroinflammatory disorders.

Importantly, the bill also standardizes dosage amounts and authorizes new delivery methods for medical cannabis, including patches, lotions, suppositories, inhalers, nebulizers, and vaping devices. The options offer flexibility in administration, catering to the diverse needs of patients with various neurological impairments.

Finally, to address the substantial logistical challenges faced by patients and physicians seeking to access the TCUP program, HB 46 increases the number of licensed medical cannabis dispensaries from three to fifteen and permits the establishment of satellite distribution locations for each licensee. This expansion aims to reduce travel burdens for patients, particularly those in the most rural and underserved areas of Texas.

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By broadening access to medical cannabis and enhancing delivery options, the legislation empowers neurologists to offer alternative therapies tailored to individual patient needs. As the state continues to evolve its approach to medical cannabis, ongoing collaboration between healthcare providers and regulatory bodies will be essential to promote patient care and ensure the responsible implementation of these new reforms.

Medigap Coverage for ALS Patients
HB 2516, introduced by Rep. Ryan Guillen (R-Rio Grande City), offered a critical step toward addressing coverage gaps for Texans living with disabilities by allowing them to purchase Medicare supplemental insurance – commonly known as Medigap plans.

Under current law, most Medigap policies are only available to individuals 65 and older, leaving many younger patients with chronic neurological conditions exposed to high out-of-pocket costs and limited provider access. HB 2516 would extend the same Medigap coverage to medically qualified patients under 65 years of age.

The Texas Neurological Society strongly supported HB 2516, recognizing its importance for patients with conditions such as ALS, multiple sclerosis, and post-stroke complications, who often face frequent specialist visits, complex therapies, and durable medical equipment needs not fully covered by Medicare alone.

Dr. Yessar Hussain, TNS board member and incoming president, came to the Capitol to testify in support of HB 2516 before the House Insurance Committee. As an expert in neuromuscular medicine and ALS care, Dr. Hussain provided compelling testimony on how the bill would improve access and continuity of care for Texans living with disabling neurological conditions.

HB 2516 passed the House and Senate with broad bipartisan support and has been sent to Governor Abbott for his signature.

Permanent Daylight Saving Time
HB 1393, authored by Rep. Will Metcalf (R-Conroe) and sponsored by Sen. Paul Bettencourt (R-Houston), would establish daylight saving time in Texas, also known as "Texas Time."

The Texas Neurological Society expressed concern about HB 1393 due to its potential impact on neurological health. Permanent daylight saving time has been associated with disruptions to circadian rhythms, leading to sleep disturbances, an increased risk of stroke, and other health issues. Dr. Reeta Achari, a board-certified sleep neurologist and TNS member, emphasized these concerns, highlighting the importance of aligning time policies with human biological clocks to promote optimal neurological function.

While the bill aims to eliminate the biannual block changes, which can certainly be disruptive, the adoption of permanent standard time is generally considered more beneficial for public health. The American Academy of Sleep Medicine and other health organizations advocate for permanent standard time, citing its alignment with natural light-dark cycles and its support for healthy sleep patterns.

While HB 1393 ultimately passed the Texas Legislature, its implementation remains contingent upon federal authorization, as current U.S. law prohibits states from independently adopting year-round daylight saving time. The Texas Neurological Society will continue to advocate for time policies that prioritize neurological health and well-being, supporting measures that align with scientific evidence and best practices in sleep medicine.

Newborn Screening for Duchenne Muscular Dystrophy
Duchenne Muscular Dystrophy (DMD) is a severe, progressive neuromuscular disorder caused by mutations in the dystrophin gene, leading to muscle degeneration and weakness. Particularly for pediatric neurologists, the early identification of DMD is critical, as timely interventions can slow disease progression and enhance overall quality of life.

SB 1044, authored by Sen. Tan Parker (R-Flower Mound) and sponsored by Rep. Giovanni Capriglione (R-Southlake), mandates the inclusion of Duchenne Muscular Dystrophy (DMD) in Texas's newborn screening program. The Texas Neurological Society was proud to support SB 1044, recognizing the importance of early diagnosis in managing neuromuscular disorders.

SB 1044 passed without opposition in both the Senate and the House and has since been signed into law by Governor Abbott.

Misleading Board Certification in Physician Advertising
Under current law, the Texas Medical Board helps ensure that physicians who advertise themselves as "board certified" have been certified by organizations meeting rigorous national standards. SB 2207, introduced by Sen. Bob Hall (R-Edgewood), would prohibit the Texas Medical Board from regulating physician advertising related to board certification.

The Texas Neurological Society joined the Texas Medical Association and other specialty societies in raising concerns over SB 2207's implications for patient safety and professional accountability. This legislation would allow physicians to claim board certification based on credentials from unrecognized or even self-designated entities, some of which lack peer-reviewed processes or substantive exams.

For neurologists, whose training involves years of advanced clinical specialization, this legislation posed a clear threat to the integrity of the specialty and the ability of patients to make informed decisions. Patients seeking neurologic care often rely on board certification as a signal of legitimate expertise. If the term "board certified" were rendered meaningless in advertising, it would increase confusion and potentially expose vulnerable patients to misleading claims.

While SB 2207 passed the Texas Senate in April, the bill ultimately died in the House Calendars Committee without being scheduled for a vote before the full house.

Graduate Medical Education (GME) Funding
The final adopted budget for the 2026-2027 biennium significantly increased support for Graduate Medical Education (GME), allocating $304.4 million in total, including $282.4 million from General Revenue and $22 million from the Permanent GME Fund. This represents a $71.3 million increase over the previous biennium.

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These investments will help preserve the state's goal of maintaining at least a 1.1-to-1 ratio of residency positions to Texas medical school graduates. The Family Medicine Residency Program received increased per-resident funding ($15,000 annually), and additional funds will support the development of new residency slots across specialties – including neurology.

TNS applauds this investment in the future physician workforce and will continue to advocate for the development of new neurology training pathways in areas of highest need.

Independent Practice for APRNs
HB 3794 by Rep. Drew Darby (R-San Angelo) and SB 3055 by Sen. Mayes Middleton (R-Galveston) proposed granting Advanced Practice Registered Nurses (APRNs) full independent practice authority, including the ability to diagnose, prescribe, and treat without physician supervision.

TNS joined a unified coalition of specialty societies to oppose these bills, emphasizing that physician-led care is crucial for managing complex neurological conditions. Without the educational and clinical training required of physicians, APRNs practicing independently would risk misdiagnosis, treatment delays, and patient harm. After hours of compelling testimony from physicians across Texas, including several members of TNS, both bills failed to advance out of their respective committees.

Health Impact, Cost & Coverage Analysis Program (HICCAP)
Authored by Rep. Jay Dean (R-Longview), HB 138 establishes the Health Impact, Cost, and Coverage Analysis Program (HICCAP) at the UT Health Science Center at Houston to assess the effects of proposed health insurance benefit mandates. TNS opposed the bill due to concerns that it could be used to delay or defeat coverage expansions necessary for emerging treatment and technologies.

Amendments adopted in the House addressed some concerns by requiring the use of peer-reviewed literature and the state's all-payer claims database and by adding the language to ensure the inclusion of public health and patient outcome data. Despite these changes, TNS remains watchful of how the tool is applied in future legislative deliberations.

Employer Choice of Benefits Plans
HB 139 by Rep. Jay Dean (R-Longview) would how allowed insurers to offer "Employer Choice" plans exempt from most state mandates and consumer protections, including network adequacy standards, prior authorization safeguards, and continuity of care provisions.

TNS joined with the Texas Medical Association, as well as other physician organization and patient advocates, to oppose this dangerous rollback of coverage protections. After a substantial floor fight led by physician lobbyists and legislative allies, Rep. Dean ultimately withdrew the bill, acknowledging that he lacked the votes to pass it.

This outcome preserves essential patient protections and affirms the legislature's commitment to strong consumer safeguards in commercial health insurance markets.

Sine Die (The End of Days)
As we turn the page on the 89th Texas Legislature, this session demonstrated once and for all that with hard work (and a little luck!), the Texas Neurological Society can deliver tangible results for the neurologists of Texas and the patients they serve. From landmark investments in research to insurance protections and medical education, the Texas Neurological Society advanced on ambitious agenda to improve neurological care in every corner of the state.

We can't close the book on this session without acknowledging our fearless leader and Legislative Chair, Dr. Kim Monday, whose vision and tireless effort powered TNS through every victory. Her leadership helped ensure that neurologists had a strong voice at the Capitol and that patient-centered care remained a top priority in health policy decisions.

We also want to thank our members, legislative allies, and the many patients and families who helped raise awareness of these issues at the Capitol. Let's build on this momentum and get ready for an even stronger showing in the interim and the 90th Legislative Session in 2027!

TNS' Lobby Day!

Our TNS crew joined more than 300 physicians, medical student, and alliance members at the Texas Capitol on Tuesday, April 1st.

A big thank you to our members who were able to participate and dedicate their time and commitment to improving the health of all Texans. We're also grateful to our lobbyist, Tom Holloway, for his ongoing dedication and hard work on behalf of TNS!

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OPEN CALL!

Serve on the 2025-2026 Independent Practice (IP) Committee

TNS offers a variety of ways for its members to become active in the society and make a difference in their profession, including participating in the IP Committee. If you are interested in joining the Independent Practice Committee, please click the "Get Involved" button below for more information.

Contact information is due by June 15, 2025

All meetings will be via ZOOM.

Get Involved

Thank You to our Women Neurologists for attending the 2025 Annual Winter Conference and Women in Neurology Happy Hour!

Be sure to check the **Women's Neurologist Section** on the TNS Website to stay in the know on future Women's Neurologist events and updates!

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REGISTRATION IS OPEN!

Early bird registration available until July 1st
Registration Deadline: July 13th, 2025

Join us at La Cantera, San Antonio this July for the TNS 2025 Summer Conference. A weekend full of clinical updates, expert insights, and dedicated tracks for both physicians AND APPs! You won't want to miss out.

REGISTER NOW!

NEURO APPs

Please join us for the first ever APP CME track at the summer TNS conference, Saturday July 19. Topics include Pearls of a Neurological Exam, Neuroimaging, and a Panel on the Collaboration between APPs and Physicians in Neurology. We are very excited to have fantastic faculty teaching these courses. We will also be having an APP Happy Hour. We would love to connect and learn how we can best serve neuro APPs in Texas!

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Supplementation Gone Awry: A Case Report of Zinc Supplementation Resulting in Copper Deficiency Myelopathy

S. Azareli Garcia Velazquez, MD[1]; Missak Tchoulhakian, DO[1] and Ratna Bhavaraju-Sanka, MD[1]
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Abstract
Copper deficiency myelopathy is a rare but potentially debilitating condition that can mimic other causes of subacute degeneration of the spinal cord. MRI findings demonstrate increase T2 signal throughout the dorsal spinal cord, a hallmark of this condition. We present the case of a patient with progressive sensory deficits, ataxia, and bladder dysfunction, initially raising concern for a neurodegenerative or autoimmune process. Laboratory testing revealed elevated serum zinc levels and profound copper deficiency, attributed to excessive zinc supplementation. Although post-vaccine myelitis is a possible consideration given symptom onset following COVID-19 and influenza vaccinations, the patient's prolonged zinc supplementation history, along with laboratory and imaging findings, strongly support copper deficiency myelopathy as the underlying cause. Despite symptom onset over a year before diagnosis, treatment with copper supplementation was initiated only after extensive testing, highlighting the risk of delayed diagnosis and potential impact on recovery. The patient was started on copper supplementation, highlighting the importance of early recognition and intervention to prevent irreversible neurological damage. Severe neurologic complications often need active intravenous copper repletion with doses 4-8 times the usual nutrition recommendations.

Introduction
Copper is an essential trace element vital for various enzymatic processes, including those necessary for proper neurological function. Copper deficiency myelopathy is a rare but serious condition that often mimics subacute combined degeneration of the spinal cord typically associated with vitamin B12 deficiency. A recent systematic review encompassing 198 cases found that the mean age of affected individuals was approximately 54 years, with a higher prevalence in females (63.8%). The most common etiologies identified were prior gastric surgery (36.2%) and excessive zinc consumption, often from zinc-containing denture creams (19.9%). A hyperintense T2 signal abnormality resembling a inverted "v" in the dorsal columns was the most common radiographic abnormality. Despite appropriate copper supplementation, only 24% of cases reported neurological improvement, and a mere 5.1% achieved full recovery. These findings underscore the importance of early recognition and intervention to prevent irreversible neurological damage (PubMed[1]) Severe neurologic complications often need active intravenous copper repletion with doses 4-8 times the usual nutrition recommendations. (PubMed[2]).

Copper plays a crucial role in maintaining the integrity of the nervous system, particularly through its involvement in mitochondrial function and myelin maintenance. Deficiency can lead to demyelination and axonal degeneration, resulting in progressive neurological symptoms. Prior studies have demonstrated that the clinical presentation of copper deficiency myelopathy closely resembles that of vitamin B12 deficiency, with overlapping features such as dorsal column dysfunction, ataxia, and corticospinal tract involvement. Given these similarities, distinguishing between these conditions is critical for appropriate management (PubMed[3])

This case report highlights a patient whose excessive zinc supplementation led to copper deficiency myelopathy, emphasizing the need for awareness of nutritional imbalances in patients presenting with myelopathic symptoms.

Case Presentation
A 63-year-old female with a history of Bartter syndrome, ulcerative colitis, and renal tubular acidosis presented with progressive numbness and loss of sensation in her extremities, balance issues, and bladder incontinence. Her symptoms began following the administration of COVID-19 and influenza vaccines. The numbness started in her feet and rapidly progressed to her hands and arms. She also reported difficulty dressing due to loss of fine motor control, episodic falls due to leg weakness, and pulsating head sensations at night disrupting sleep. Additionally, she had a history of frequent bladder infections and temperature dysregulation, experiencing worsening mobility in cold temperatures and near-syncope in hear.

On neurological examination, cranial nerves were intact with normal speech and comprehension. Motor strength was 5/5 throughout except for 4+ dorsiflexion at the ankles. Deep tendon reflexes were brisk with a crossed adductor response, 1-beat clonus, and a positive Hoffman sign. Sensory examination revealed patchy loss of pinprick sensation up to T10, worse anteriorly than posteriorly. Vibration sensation was reduced in the lower extremities, and position sense was absent in the toes. She demonstrated severe ataxia with impaired heel-to-shin and finger-to-nose testing, as well as an ataxic gait.

Imaging and Diagnostic Tests
- *MRI Cervical and Thoracic Spine:* Increased T2 signal throughout the dorsal aspect of the spinal cord spanning C2-C6 and central thoracic spinal cord from T1 to T11. No postcontrast enhancement to suggest tumor or infection.
- *Nerve Conduction Studies:* Normal. No clinical or electrophysiological evidence to support focal tibial, peroneal, or sciatic neuropathy, peripheral polyneuropathy, lumbar plexopathy, radiculopathy, or myopathy or the lower extremities (12/2024).
- *Skin Biopsy:* Mildly reduced nerve fiber density in the upper thigh at 5.9 per millimeter (normal >7). Lower thigh normal at 6.7 (normal >6). Lower calf normal at 4.5 (normal >3.2).
- *CSF analysis:* unremarkable, with normal protein and cell count. Serum MOG and NMO antibody tests were negative.
- Serum B12 levels were normal, and ceruloplasmin was elevated.
- Significantly low serum copper (12.1 µg/dL; reference rang: 70-140 µg/dL) and elevated serum zinc (126 µg/dL; reference range: 60-120 µg/dL). The patient reported taking daily zinc supplements for the last two years, further supporting the role of chronic zinc over-consumption in inducing copper deficiency myelopathy.

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Supplementation Gone Awry: A Case Report of Zinc Supplementation Resulting in Copper Deficiency Myelopathy

Continued...

Discussion

Copper deficiency myelopathy is a rare but serious condition that is often misdiagnosed as a demyelinating disorder, such as multiple sclerosis, or a metabolic disorder, such as vitamin B12 deficiency. Zinc overconsumption is a well-known yet frequently overlooked etiology, as excessive zinc intake disrupts copper absorption in the gastrointestinal tract. Early diagnosis is crucial, as prolonged copper deficiency can result in irreversible neurological damage. In the current era, there is a tendency to attribute all neurological symptoms to COVID-19 infection or vaccination, which may lead to delays in identifying alternative causes such as nutritional deficiencies. While treatment with copper supplementation may improve symptoms, many patients experience only partial neurological recovery. Despite supplementation, our patient has not noticed significant subjective improvement, though there has been minimal strength improvement. Given this, her oral copper supplementation has been increased from 2 mg to 4 mg.

This case also highlights the risks associated with excessive supplementation. The patient has been taking zinc supplements to prevent viral infections and boost her immune system, unaware of the potential for toxicity. This underscores the need for better education regarding the dangers of over-the-counter supplements, as unchecked consumption can lead to severe neurological consequences.

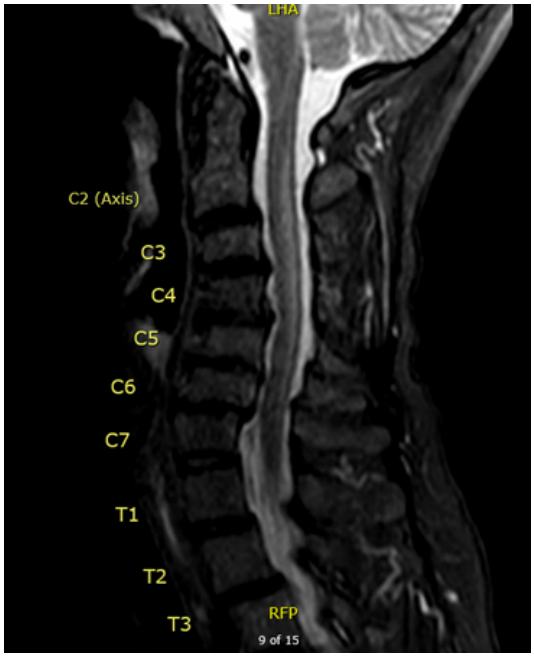

Figure 1. *Contiguous T2 hypersensitivity involving the dorsal aspect of the spinal cord spanning C2-C6 vertebral body levels on MRI sagittal STIR imaging.*

Conclusion

This case underscores the importance of recognizing nutritional deficiencies as a cause of progressive myelopathy. Clinicians should have a high index of suspicion for copper deficiency in patients with subacute ataxia, sensory deficits, and elevated zinc levels. Early intervention with copper supplementation may improve outcomes and prevent permanent disability.

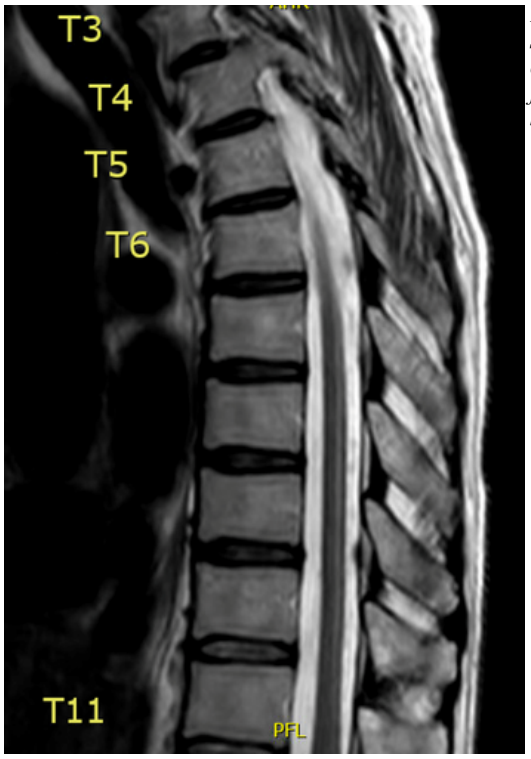

Figure 2. *Increased T2 signal throughout the central thoracic spinal cord from T1 to T11 vertebral body level on MRI sagittal T2 imaging.*

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The Smile That Faded: Delayed-Onset Facial Weakness Following Severe Traumatic Brain Injury

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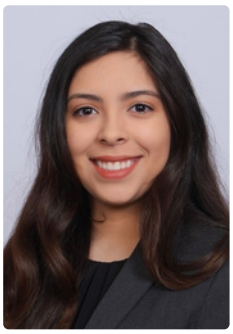

Introduction

An estimated sixty-nine million traumatic brain injuries (TBI) occur worldwide per year, with North America having the highest per 100,000 people (1). A traumatic brain injury (TBI) can be classified as either open or closed, where the patient doesn't have any penetrating wounds in the dura. The severity is classified by using 4 different criteria: duration of unconsciousness, structural imaging (CT/MRI), duration of post-traumatic amnesia, and the Glasgow Coma Scale. Traditionally the Glasgow Coma Scale is used by various neurosurgeons for assessing and predicting risk of mortality. However, it is limited in accurately assessing patients that require mechanical ventilation as it cannot measure verbal response if the patient is intubated, take into consideration brain stem reflexes, or breathing patterns. Assessing these considerations is crucial in intensive care unit (ICU) settings where a majority of severe TBI patients receive care (2). A second type of assessment, the Full Outline of Unresponsiveness (FOUR) score, was validated through multiple studies to accurately assess mortality in patients with TBI and has been used within facilities across the nation, including the Neurology Intensive Care University at the University of Texas Medical Branch-Galveston (UTMB) (3-6).

Roughly 3.2 million people that survived a TBI in the United States in 2008 experienced varying degrees of disability following the incident, including sensory and motor loss, impaired cognitive function and autonomy, decreased confidence, and altered social aspirations (7). Those with severe disabilities can be left unable to maintain employment, which in turn may increase psychosocial and socioeconomic stressors. These stressors compounded with the difficulty of the 76.5 billion dollar lifetime medical cost associated with care following TBI can impact the patients life significantly (8).

Here we describe a patient who initially presented to the UTMB trauma center shortly after a motor vehicle accident and again 1 year later in a neurology clinic with an unexpected clinical presentation given the characteristics of the original brain injuries and an altered sense of self.

Case Report

A 25-year-old African-American woman experienced a motor vehicle accident in which the vehicle collided into a guardrail on the highway. After exiting the vehicle, she was subsequently hit by a second vehicle that was driving at an approximate speed of 65 miles per hour. The patient was found by EMS about 150 feet away from her own vehicle unconscious, with right eye proptosis, bilateral fixed and dilated pupils, a right open chest wound, and bilateral open femur fractures. Patient became hemodynamically unstable after a significant drop in her heart rate while in transit to the nearest trauma center, which was then rerouted for higher level of care at UTMB for Level 1 Trauma activation. The patient became pulseless and received cardiopulmonary resuscitation while in transit before she had return of spontaneous circulation four minutes later. A cervical collar, bilateral chest tubes, 7.5 endotracheal, 1 unit of uncrossed RBCs infusing to gravity, epinephrine drip infusing at 0.3/mcg/kg/min, and ketamine were given in the field by EMS. On arrival, the patient was 3T on the GCS. Following an exploratory laparotomy with surgical repair on a liver laceration, the patient received a postoperative head CT without contrast (Figure 1). The CT was suspicious for orbital compartment syndrome and revealed an occipital subgaleal hematoma. No hydrocephalus, midline shift, pathological extra-axial fluid collection, intracranial hemorrhage, or parenchymal attenuation abnormality was identified. Neurosurgery ruled out the need for immediate neurosurgical intervention.

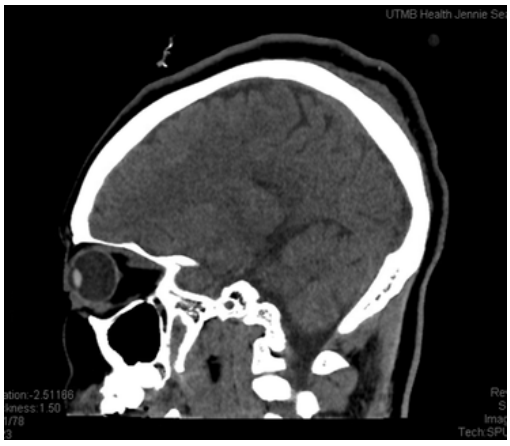

Figure 1. *Head CT without contrast with occipital subgaleal hematoma*

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Continued...

Hospital Day 1
The general neurology physical exam was measured with the FOUR score. Patient was sedated with fentanyl 25 mcg during the exam. She scored a 3 for eye response, 3 for motor response, 4 for brainstem reflexes and 1 for respiration. Her right extremities were spontaneously moving more than her left.

Hospital Day 2
The neurology physical exam was measuring with the FOUR score while the patient was receiving fentanyl 25 mcg, which revealed worsening neurologic function with 0 for eye response, 0 for motor response, 0 for brainstem reflexes, and 1 for respiration. She had an abnormal EEG indicating the presence of moderate degree of encephalopathy and Frontal Intermittent Rhythmic Delta Activity (FRIDA), which can be suggestive of a global or subcortical cerebral dysfunction secondary to nonspecific etiology.

Hospital Day 3
Patient showed an improved FOUR score, with 2 for motor response. This is consistent with the patient withdrawing to noxious stimuli, with other scores remaining unchanged. The patient was on fentanyl 25 mcg during the exam.

MRI was completed due to the patient remaining unconscious with minimal improvement of the FOUR score (Figure 2A-B). Results showed multifocal areas of supratentorial diffusion restriction with correlating T2/FLAIR hyperintensities with similar changes noted in the bilateral cerebellar hemispheres, corpus callosum, bilateral hippocampi, bilateral internal capsule and right caudate nucleus. This may represent a combination of hypoperfusion infarcts and metabolic encephalopathy with possible extrapontine myelinolysis. Scattered cortical T1 hyperintensity in the gradient blooming signal noted in the right frontal and bilateral parietal lobes may represent petechial hemorrhage. Punctate petechial hemorrhage is also noted in the bilateral cerebellar hemispheres. No hydrocephalus or midline shift. No acute neurosurgical intervention was necessary, and the neurology team signed off at this point.

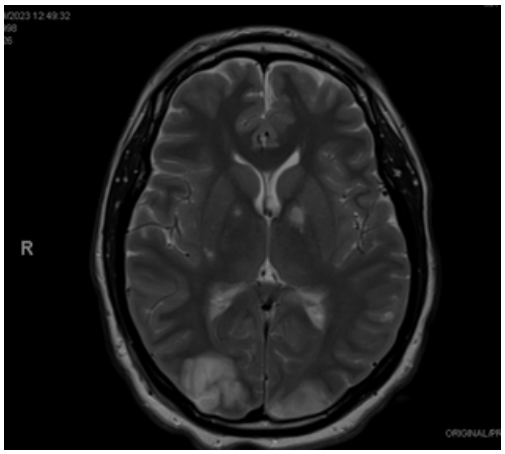

Figure 2A. *Head MRI with hyperintensities in the corpus callosum, bilateral hippocampi, bilateral internal capsule and right caudate nucleus.*

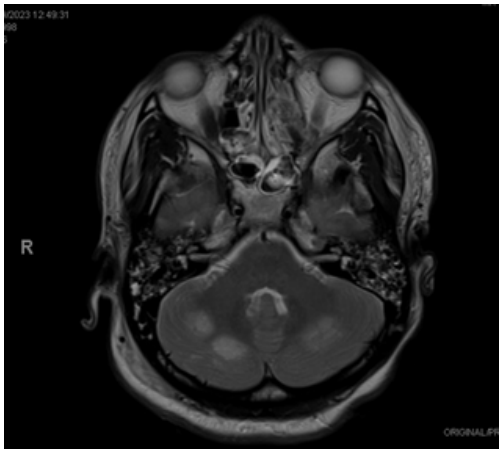

Figure 2B. *Head MRI with hyperintensities in the bilateral cerebellar hemispheres.*

Throughout the rest of her hospital admission, information of her neurological examination was limited based on available electronic medical record documentation. The patient was able to spontaneously open her eyes on hospital day 5. She was able to follow commands intermittently on hospital day 6. The patient was able to follow commands continuously on hospital day 7. Patient was discharged on hospital day 46 due to repairs of other trauma-related injuries. On discharged, she was stable neurologically. She was alert, oriented and verbally responsive. Her cranial nerves were intact. She did have decreased strength of her right lower extremity due to trauma related tibial fracture.

Outpatient Evaluation
One year after initial admission, the now 26 year old patient arrived at the outpatient neurology clinic to discuss her new neurological baseline. The patient described a new onset of facial weakness that had been occurring for one month. On the physical exam cranial nerves were intact except for weakness in cranial nerve VII, and the mandibular branch of the trigeminal nerve. Patient was unable to form a smile or pucker her lips. Patient was also unable to depress her mandible to a significant degree, resulting in difficulty eating. There was no difficulty elevating her mandible. She was able to move the upper half of her face freely for 5/5 frontalis strength. She did have facial symmetry with no obvious drooping of the corners of her mouth, eyelids or flattening of the nasolabial fold. When the patient's mandible was manually opened, the patient did have symmetric palatal elevation and midline protrusion of the tongue. The patient denied having changes with taste, dysarthria, and dysphagia.

Head CT without contrast revealed scatter hypodensities seen in the cortical and deep white matter that correspond to some of the lesions seen on prior MRI and no acute findings (Figure 3A-C).

Outside of the weakness of her mouth and jaw, she was experiencing mild issues with short term memory and somber mood. She reported having to ask the same question multiple times and forgetting the names of her friends and family. The patient scored a 28/28 on her Mini Mental Status Exam. The short term memory issues and other trauma related injuries have impacted her life negatively. The patient is no longer trusted by her family to drive her vehicle, as they are afraid she could get lost or have physical weakness with driving.

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She has been unable to return to her place of work due to the physical demands necessary for daily activities. She has felt a loss of autonomy since the accident. Moreover, this new complaint of inability to smile or be expressive has decreased her confidence overall.

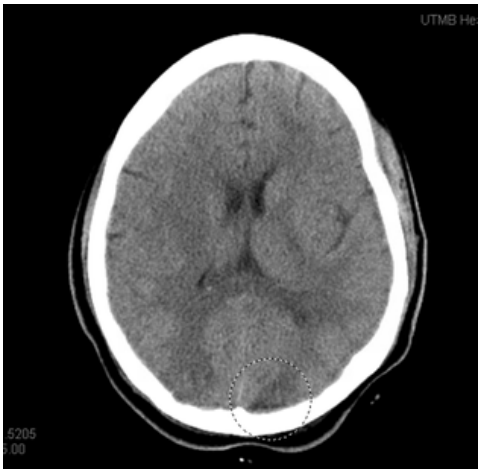

Figure 3A. *Head CT without contrast with occipital lobe hypodensity.*

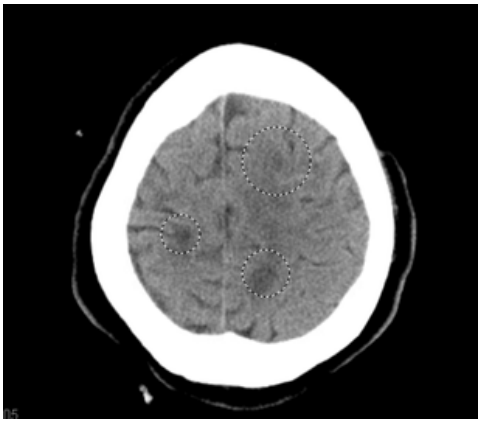

Figure 3B. *Head CT without contrast with scattered hypodensities in the cortical and deep white matter of both cerebral hemispheres.*

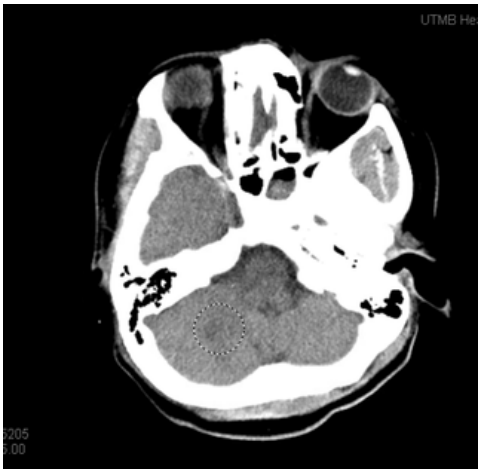

Figure 3C. *Head CT without contrast with cerebellar hypodensity.*

Discussion

At one-year post-traumatic brain injury, most patients experience stabilization in cognitive and functional recovery, with minimal to no new symptoms in the absence of new structural findings on imaging (9). This patient's inability to open her jaw or smile for one month represents an unusual clinical presentation, especially given the absence of new infarcts or hemorrhages on her most recent CT imaging. Typically, recovery at this stage is characterized by a plateau in cognitive and motor improvements rather than new deficits. Although delayed symptoms are possible following TBI, they are generally associated with secondary complications such as seizures, hydrocephalus, or progressive neurodegeneration, none of which were present in this case. Her severe initial presentation, including prolonged unconsciousness, fluctuating FOUR scores and EEG findings of moderate encephalopathy and FRIDA, may have contributed to a prolonged or abnormal recovery course. However, the exact mechanism underlying this delayed symptom remains uncertain and an area to further explore the diverse possibilities of long-term symptoms of TBI.

Beyond the immediate recovery phase, individuals with TBI face an increased risk of developing long-term comorbidities. A cohort research study published in *JAMA Network Open* shows that patients who have experienced a TBI were more likely to develop cardiovascular and endocrine disorders compared to those without a history of TBI (10). Furthermore, a systematic review in *BMJ Open* emphasizes that comorbid conditions significantly impact both short-term and long-term outcomes, including a higher risk of mortality (11).

Given the patient's young age, the impact of traumatic brain injury (TBI) on her social life is a significant concern due to the potential for long-term side effects. Young adults with TBI often experience substantial challenges in social participation, which can negatively affect their quality of life and psychosocial well-being. Research indicates that individuals with TBI frequently struggle with interpreting social cues, maintaining relationships, and engaging in social interactions, which may lead to social withdrawal and isolation. It is also common within these individuals to go through emotional adjustments such as increased anxiety and depression and can possibly hinder rehabilitation progress as well as overall life satisfaction (12). These difficulties are particularly highlighted in younger adults, who are already navigating critical stages of personal and social development. Addressing these social and emotional challenges through targeted interventions is essential to support the patients long-term recovery and reintegration into society.

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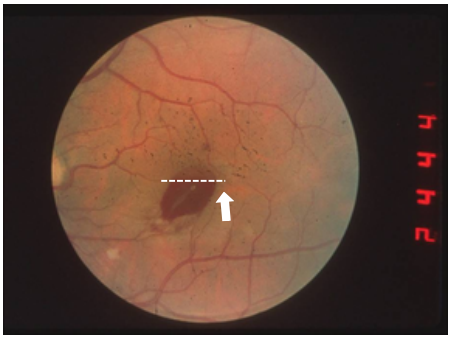
Retinal Sub-Hyaloid Hemorrhage: A Hitherto Unreported Finding in Sub-Acute Bacterial Endocarditis

Kalarickal J. Oommen, MD

Case Report

The patient was a 36-year-old woman without significant medical history who developed headache and blurring of vision. She was seen by her primary care physician who treated her headaches with analgesics and referred her to an ophthalmologist because of her blurring of vision. The examination of her eyes revealed what is seen in Image 1 or the right. The ophthalmologist immediately referred the patient to the University Medical Center's Emergency Room (ER) for evaluation of possible subarachnoid hemorrhage (SAH). When seen in the ER, the patient reported intermittent headaches with blurring of vision lasting 4-6 hours which she managed with Tylenol. She had no prior history of motor vehicle accidents or of head trauma. She denied any prior medical illness. Specifically, there was no history of migraines or sudden "explosive" headache as is so often reported by patients with SAH.



On examination in the ER, she was in no acute distress and her vitals were normal except for her temperature of 99.9°F. Her general physical examination was normal and there was no evidence of external trauma. Her complete blood count (CBC), Chemistry 12 and urinalysis were normal except for mild anemia and an elevated erythrocyte sedimentation rate (ESR).

Neurology was consulted. Ophthalmoscopy revealed an oval lesion in the retina in one eye with a fluid level separating dark brown blood below and clear serum above as shown in Image 1. Her neurological examination was otherwise normal. Her CT of the head was normal. She was admitted to neurology for further evaluation.
...What is your Diagnosis?

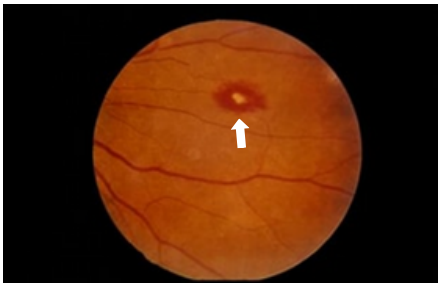
Retinal Sub-Hyaloid Hemorrhage

Because of the fever and increase erythrocyte sedimentation rate (ESR), two blood cultures were ordered 12 hours apart. The cultures were positive and the bacterium was identified as streptococcus viridans. An echocardiogram was positive for valvular vegetations. Based on the positive blood cultures and the vegetations on echocardiogram a diagnosis of subacute bacterial endocarditis (SBE) was made.

SBE is an infection of the blood and can be caused by several bacteria and other infectious agents such as staphylococcus aureus, streptococcus, gallotyticus, coagulase negative staphylococci, HACEK organisms, (the acronym derived from hemophilus, aggregatibacter, cardiobacterium, ekinella and kingella) and enterococci, although penicillin sensitive streptococcus viridans is the most common cause of SBE. Other rarer organisms include pneumococci, candida, gram-negative bacilli, and polymicrobial organisms.

SBE is a slower disease process compared to the acute form caused by staphylococcus aureus, a febrile illness that rapidly damages cardiac structures and spreads hematogenously and can cause progression to death within weeks from cardiac or multiorgan failure or sepsis if not treated expeditiously.

SBE can be difficult to diagnose, but some risk factors such as age over 60 years, male gender, IV drug use, prior infective endocarditis, poor dentition or recent dental procedure, presence of a prosthetic valve, intracardiac device or indwelling venous catheter, valvular heart disease, congenital heart disease, presence of immunosuppression and hemodialysis in the history and physical findings such as heart murmurs, Roth's spots, Osler's nodes and Janeway lesions when present on physical examination can help with choosing the appropriate investigatory pathway to reach a conclusive diagnosis of SBE.



Roth spots are tiny round retinal hemorrhages with a white spot in the center and are often referred to as hemorrhagic cotton-wool exudates. Once considered pathognomonic of SBE (see Image 2), it is now considered non-specific, seen in multiple systemic conditions of various etiologies. Osler nodes are red-purple, slightly raised, tender lumps, often with a pale center, frequently preceded by pain up to 24 hours before the visible lesion, typically found on the fingers and or toes. They can occur at any time during the course of SBE and last from hours to several days. It is know to the French before Osler as *Nodosites Cutanees Ephemeres* meaning 'Cutaneous nodules of short duration', but is is known after him as he was the first to explain its clinical significance. Janeway lesions are flat painless hemorrhagic skin lesions and are more common in acute bacterial endocarditis. Although Roth's spots, Osler nodes and Janeway lesions have a well-known association with SBE, this is the first case of sub-hyaloid hemorrhage in SBE, known to this author. Antibiotic treatment should be prompt, guided by culture and sensitivity.

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New Anticoagulants in Clinical Practice: A Comprehensive Review for Neurologists

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Introduction

Anticoagulation therapy has undergone a profound evolution over the past two decades. Traditionally, vitamin K antagonist (VKAs) such as warfarin and low molecular weight heparin (LMWH) dominated therapeutic strategies for preventing thromboembolism. However, the development and introduction of direct oral anticoagulants (DOACs) have transformed clinical practice by offering more predictable pharmacokinetics, fewer food and drug interactions, and reduced need for routine laboratory monitoring.

The transition to DOACs has not been without challenges. As new evidence emerges from randomized controlled trials (RCTs), real-world registries, and meta-analyses, clinicians must navigate nuances involving efficacy, safety, cost, patient adherence, and appropriate application across a wide range of patient populations. Neurologists, in particular, must balance thromboembolic prevention with hemorrhagic risk in conditions such as nonvalvular atrial fibrillation (NVAF) and perioperative settings. This review synthesizes the latest evidence, guideline recommendations, and practical considerations for the use of new anticoagulants in clinical practice.

Direct Oral Anticoagulants: Pharmacy and Mechanisms

DOACs currently available include four factor Xa inhibitors - rivaroxaban, apixaban, edoxaban, and betrixaban - and one direct thrombin inhibitor, dabigatran. Their pharmacologic characteristics are summarized in Table 1. Unlike VKAs, these agents offer rapid onset and offset of action, standardized dosing, and do not require INR monitoring. However, plasma levels are not reliably assessed by standard coagulation assays such as PT and aPTT, necessitating specialized assays in select clinical scenarios, such as emergency surgery or major bleeding events.

The American Heart Association (AHA), American College of Cardiology (ACC), and Heart Rhythm Society (HRS) 2019 update, alongside the 2020 European Society of Cardiology (ESC) atrial fibrillation guidelines, recommend DOACs are the preferred agents for stroke prevention in NVAF absent mechanical valves or moderate to severe mitral stenosis. The CHEST 2021 VTE guidelines similarly endorse DOACs over VKAs for venous thromboembolism (VTE) treatment when possible.

Stroke Prevention in Nonvalvular Atrial Fibrillation

The role of DOACs in NVAF is well established through multiple pivotal trials. In ARISTOTLE, apixaban demonstrated a 21% reduction in the combined endpoint of stroke or systemic embolism compared to warfarin, alongside a 31% reduction in major bleeding. Similarly, the RE-LY trial showed dabigatran 150 mg reduced ischemic stroke by 34% compared to warfarin, with comparable or lower rates of hemorrhagic complications. The ROCKET-AF trial confirmed noninferiority of rivaroxaban to warfarin, while ENGAGE AF-TIMI 48 found both high- and low-dose edoxaban regimens noninferior, with less major bleeding.

Table 1. General Information for the five DOACs

Generic	Rivaroxaban	Apixaban	Edoxaban	Betrixaban	Dabigatran
Brand(s)	Xarelto®	Eliquis®	Savaysa® Lixiana®	Bevyxxa®	Pradaxa®
Target	FXa	FXa	FXa	FXa	Flla
Antidote	Andexanet alfa (Ondexxya®)	Andexanet alfa (Ondexxya®)	None	None	Idarucizumab (Praxbind®)
Creatinine Clearance*	>50 mL/min	>50 mL/min	>50 mL/min	>30 mL/min	>30 mL/min
Renal Excretion	33%	27%	50%	11%	80%
Half-Life (h)	5-13	12	10-14	19-27	12-27
Oral Bioavailability	80%	50%	62%	34%	3-7%
Time to C_{max} (h)	2-4	3-4	1-2	3-4	2
Volume of Distribution (L)	55	21	107	32	50-70
Protein Binding	95%	87-93%	55%	60%	35%
CYP450 Metabolism	Yes	Yes	Minimal	Minimal	No
P-gp substrate	Yes	Yes	Yes	Yes	Yes

**Creatine clearance (CrCL) calculated by the Cockcroft-Gault formula. Dosages will need to be adjusted for patients with moderate renal impairment.*

A 2020 meta-analysis of 12 randomized controlled trials consolidated these findings, demonstrating that DOACs reduced the risk of stroke or systemic embolism by 19%, intracranial hemorrhage by 51%, and all-cause mortality by 10% compared with warfarin (Ruff et al., *Lancet,* 2020). These results have been reinforced by real-world registries such as ORBIT-AF II and GARFIELD-AF, which consistently show favorable outcomes for DOACs across diverse populations.

Venous Thromboembolism Treatment and Extended Prevention

The treatment of acute VTE and DOACs has been validated through the EINSTEIN-DVT and EINSTEIN-PE studies for rivaroxaban, the AMPLIFY study for apixaban, the Hokusai-VTE study for edoxaban, and the RE-COVER studies for dabigatran. These trials established noninferiority to standard therapy, with some agents demonstrating lower rates of major or clinically relevant nonmajor bleeding.

For extended prophylaxis, the EINSTEIN-Extension and AMPLIFY-EXT trials demonstrated that continued rivaroxaban or apixaban therapy reduced recurrent VTE without significant increases in major bleeding. RE-SONATE and RE-MEDY similarly showed that dabigatran extended therapy lowered VTE recurrence but was associated with higher nonmajor bleeding compared to placebo.

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Special Populations

New data continue to emerge regarding the use of DOACs in special populations. In cancer-associated thrombosis (CAT), the Hokusai VTE-Cancer trial demonstrated that edoxaban was noninferior to dalteparin, though with increased bleeding risk in gastrointestinal malignancies. SELECT-D similarly supported rivaroxaban use in CAT, again cautioning increased bleeding in certain cancer types. These findings have led to revised ASCO and ISTH guidelines recommending selected DOACs as acceptable options in CAT.

In patients with obesity, analyses from the Dresden NOAC Registry and post-hoc data from ARISTOTLE suggest that DOACs maintain efficacy and safety even in individuals with BMI >40 or body weight >120 kg. Similarly, subgroup analyses in elderly patients, such as those from ENGAGE AF-TIMI 48, have affirmed the benefits of DOACs without significant excess bleeding.

Renal dysfunction remains a key consideration. Apixaban has emerged as the DOAC least affected by moderate renal impairment, while dabigatran, with its 80% renal clearance, requires caution and dose adjustment.

Procedural and Perioperative Management

Careful perioperative planning is crucial for patients on DOAC therapy. Elective neurosurgery and high-bleeding-risk interventional pain procedures typically necessitate holding DOACs for two to four days depending on renal function and bleeding risk. For emergency situations, idarucizumab provides rapid reversal of dabigatran, while andexanet alfa serves as a reversal agent for apixaban and rivaroxaban. Ciraparantag (PER977), an investigational agent showing promise for universal reversal of DOACs and heparins, remains under clinical evaluation.

Valvular Heart Disease Considerations

While DOACs are contraindicated in patients with mechanical heart valves following the RE-ALIGN trial findings, their role in bioprosthetic valve recipients is evolving. The RIVER trial demonstrated that apixaban was noninferior to warfarin for stroke prevention in patients with bioprosthetic mitral valves and atrial fibrillation. Similarly, the ENVISAGE-TAVI AF trial found edoxaban to be comparable to warfarin post-TAVI, although with higher bleeding rates, warranting caution in these settings.

Limitations and Challenges

Despites their advantages, DOACs present several limitations. Adherence is critical given their short half-lives; missed doses can quickly lead to loss of anticoagulant effect. Cost remains a barrier for many patients, particularly those uninsured or underinsured, despite evidence suggesting overall healthcare savings through reduced monitoring and fewer bleeding complications. Off-label use, especially in populations with mechanical valves or antiphospholipid syndrome, carries significant risk and must be approached with caution.

Future Directions

The next frontier in anticoagulation may be represented by factor XI inhibitors, such as abelacimab, osocimab, and asundexian, which aim to uncouple thrombosis prevention from bleeding risk. Early phase trials are promising, and larger Phase III studies are ongoing. Expanded availability of universial antidotes like ciraparantag could further streamline emergency management of anticoagulation.

Conclusion

The advent of direct oral anticoagulants has fundamentally reshaped the practice of anticoagulation, offering clinicians safer, simpler, and often more effective alternatives to traditional therapies. However, optimal use demands familiarity with the latest clinical evidence, guideline recommendations, patient-specific factors, and emerging therapeutic options. As research continues to evolve, neurologists and allied specialists must remain informed to deliver anticoagulation care that is not only evidence-based but also tailored to individual patient needs.

Key Points Summary

- **Direct oral anticoagulants (DOACs)** have replaced vitamin K antagonists as the preferred option for most patients with nonvalvular atrial fibrillation (NVAF) and venous thromboembolism (VTE).
- **Major randomized trials** (ARISTOTLE, RE-LY, ROCKET-AF, ENGAGE AF-TIMI 48) and **meta-analyses** demonstrate DOACs have superior safety profiles, especially lower rates of intracranial hemorrhage.
- **Real-world registries** (ORBIT-AF II, GARFIELD-AF) confirm these findings in broader populations, including elderly and patients with renal impairment.
- **Special populations** such as cancer-associated thrombosis (CAT) and obese patients now have emerging data supporting DOAC use (Hokusai VTE-Cancer, SELECT-D).
- **Reversal agents** like idarucizumab and andexanet alfa exist for emergency management; investigational antidotes like **ciraparantag** are under development.
- **Bioprosthetic valves and TAVI patients** may benefits from DOACs based on new trials (RIVER, ENVISAGE-TAVI AF), but caution is required.
- Limitations include **adherence challenges, higher costs, drug-drug interactions,** and **contraindications** in mechanical valve or antiphospholipid syndrome patients.
- **Future directions** include factor XI inhibitors (abelacimab, asundexian) promising thrombosis prevention with less bleeding.

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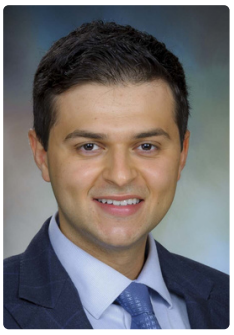
Leptomeningeal Myelomatosis in a Patient with Multiple Myeloma: A Case Report and Literature Review



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Abstract

Objective: We present the case of a 67-year-old patient with a history of multiple myeloma, who developed focal neurological symptoms initially attributed to a transient ischemic attack (TIA) but later found to be secondary to leptomeningeal myelomatosis.

Background

Patients with multiple myeloma, especially those undergoing complex treatment regimens such as chemotherapy, CAR-T therapy, and novel agents such as talquetamab for refractory MM, are susceptible to central nervous system (CNS) complications. These complications may arise from disease progression, treatment-related toxicity, or cerebrovascular events. CNS involvement by multiple myeloma is rare but carries a poor prognosis. Identifying and distinguishing between different neurological causes is essential for targeted intervention. Contrast enhanced imaging can help differentiate these causes as it can reveal leptomeningeal involvement. Leptomeningeal myelomatosis is a rare complication of multiple myeloma (occurring in <1% of patients) characterized by the spread of malignant plasma cells to the central nervous system. This condition can present with diverse neurological symptoms and may mimic other pathologies, such as stroke or paraneoplastic syndromes and historically carries a very poor prognosis.

Case Presentation with Discussion

A 6-year-old male with a history of hypertension, pulmonary embolism, Meniere's disease and Multiple Myeloma on taquel-temab presented as the subject of a stroke alert due to transient word-finding difficulty. MRI of the brain without contrast showed no acute intracranial abnormalities, and he was discharged on aspirin and statin for presumed TIA. However, he subsequently represented two weeks later with worsening gait instability, headaches, and transient dysarthria with receptive aphasia. Neurological examination revealed transient attention deficits and wide based gait, but no other pathologic findings. Given his history, a broad differential was considered, including leptomeningeal myelomatosis, paraneoplastic syndromes, brain metastasis, seizures, immune effector cell-associated neurotoxicity, and talquetamab-related neurotoxicity.

MRI of the brain with contrast was obtained and revealed diffuse leptomeningeal enhancement, raising concern for leptomeningeal disease or infectious meningitis. Lumbar puncture confirmed the diagnosis of leptomeningeal myelomatosis, revealing a kappa-restricted plasma cell population comprising 87% of total cells. The infectious workup, including a meningoencephalitis nucleic acid amplification test panel, was negative. MRI of the spine later obtained which also revealed diffuse dural enhancement. Treatment shifted towards addressing leptomeningeal myelomatosis, however, the patient passed away in the following weeks.

Conclusion

CNS myelomatosis, though rare, should be considered in Multiple Myeloma patients presenting with neurological deficits. Early diagnosis though contrast enhanced imaging and cerebrospinal fluid analysis is critical for timely intervention and optimizing patient outcomes.

Introduction

Multiple myeloma is a hematologic malignancy characterized by the proliferation of clonal plasma cells. Neurological symptoms in such patients may be multifactorial, including disease progression, paraneoplastic syndromes, drug-related effects, cerebrovascular events, and metastatic disease. While extramedullary disease is well-recognized, CNS involvement, including leptomeningeal myelomatosis, is rare and associated with poor prognosis. Additionally, novel agents like talquetamab, a bi-specific antibody targeting GPRC5D and CD3, have revolutionized treatment but can introduce unique adverse effects, including neurotoxicity. Identifying and distinguishing between different neurological causes is essential for targeted intervention. Contrast enhanced imaging can help differentiate these causes when a patient with a history of malignancy presents with neurological deficits as it can reveal leptomeningeal involvement. This report details a challenging case of neurological deterioration in a patient receiving talqutamab for refractory MM, initially diagnosed with TIA but ultimately confirmed to have leptomeningeal myelomatosis.

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Case Presentation

A 67-year-old male with a history of multiple myeloma, hypertension, pulmonary embolism, and Meniere's disease was admitted after a stroke alert due to transient word-finding difficulty. MRI of the brain without contrast showed no acute intracranial abnormalities, and he was discharged on aspirin and statin for presumed TIA. Two weeks after discharge, he experienced progressive gait instability, worsening headaches, and recurrent transient dysarthria with word-finding difficulty and receptive aphasia. On neurological examination, transient attention deficits were noted and wide based gait, but no other focal deficits were present.

At that point, differential diagnosis included paraneoplastic syndrome, brain metastasis, infectious meningitis, non-convulsive seizures, Taquel-tamab induced neurotoxicity and leptomeningeal myelomatosis. Imaging did not reveal any intra-axial massess and CSF was negative for a meningio-encephalitis on nucleic acid amplification test panel. Taquel-tamab induced neurotoxicity, specifically ICANS, was deemed less likely due to timing of symptom onset. Continuous EEG showed generalized slowing with intermittent focal slowing in the left temporoparietal lobe, without any epileptiform discharges. Lastly, MRI Brain and whole spine with and without contrast showed extensive leptomeningeal enhancement in supratentorial and infratentorial regions, scattered cervical dural enhancement, thoracic focus of enhancement, and cauda equina leptomeningeal enhancement. CSF cytology revealed 87% kappa-restricted plasma cells, confirming leptomeningeal myelomatosis.

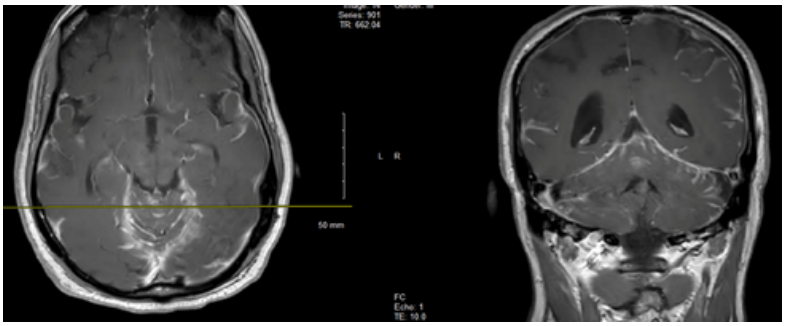

Figure 1: *MRI brain w/wo (T1 post axial, T1 post coronal)*

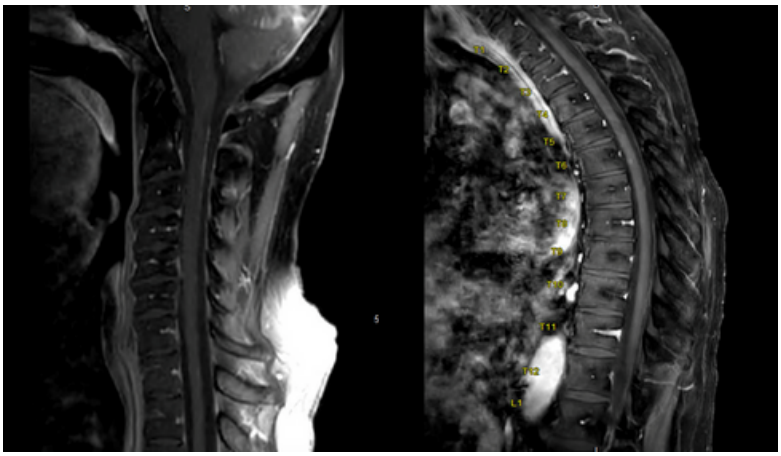

Figure 2: *MRI C spine w/wo (T1 sagittal post)*

Figure 3: *MRI T spine w/wo (t1 sagittal post)*

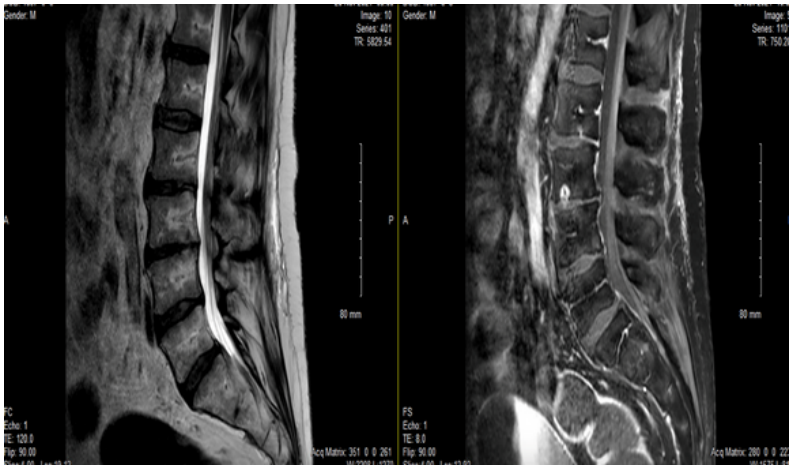

Figure 4: *MRI L Spine w/wo (T2 sagittal, T1 post)*

Taqueltamab was initially discontinued given potential concerns of neuro-toxicity and the patient's home levetiracetam was increased to 1500mg BID given concern for left focal temporoparietal seizures given transient word-difficulty episodes. Pt was referred to neuro-oncology for management of CNS myelomatosis who recommended combination targeted-therapy with Selinexor, bendamustine, elranatamab, as well as intrathecal chemotherapy. Unfortunately, the patient developed drug induced liver injury from one dose of Selinexor and eventually neutropenic fever. The patient's family opted for hospice care where the patient expired two weeks later.

Discussion

This case ultimately illustrates the diagnostic challenge posed by Leptomeningeal myelomatosis, which is an uncommon but devastating manifestation of multiple myeloma, occurring in less than 1% of cases. Comparisons with previously reported cases indicate that patients often present with progressive neurological symptoms such as cranial nerve deficits, cognitive decline, and seizures. As demonstrated, the diagnosis is confirmed through MRI and CSF cytology. In this case, the presentation was initially subtle, resembling a TIA, which is an uncommon but previously described diagnostic pitfall. Talquetamab, a novel bispecific antibody, is associated with neurotoxicity, including headaches (20%) and dysarthria/gait abnormalities (11%) and for this reason it was held along with a potential concern for Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) by hematology. However, ICANS would not present as transiently and typically occurs soon after the initiation of the therapy rather than later in the treatment course. The distinction between drug-related effects and disease progression is critical, as misattributing symptoms could delay appropriate management.

The presence of extensive supratentorial and infratentorial leptomeningeal involvement in this patient underscores the need for vigilance when neurological symptoms emerge in multiple myeloma patients. Given the rarity of CNS myelomatosis, its pathophysiology remains incompletely understood, though it likely arises from hematogenous or direct extension of plasma cells. Myelomatosis often requires aggressive treatment, with a median survival of only a few months following dianosis; current treatment strategies are limited, often involving intrathecal chemotherapy

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(methotrexate, cytarabine) or systemic therapies capable of crossing the blood-brain barrier, though prognosis also remains poor. Radiotherapy may be used for focal symptom control, but outcomes remain disappointing. Continued research into targeted CNS-penetrant therapies is necessary to improve outcomes.

Conclusion

CNS myelomatosis, though rare, should be considered in Multiple Myeloma patients presenting with neurological deficits. Early diagnosis through contrast enhanced imaging and cerebrospinal fluid analysis is critical for timely intervention and optimizing patient outcomes.

Disclosure Statement

The authors have no financial or other disclosures to include.

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Types of SCS (Spinal Cord Stimulation): A Comparative Analysis of Efficacy and Mechanism

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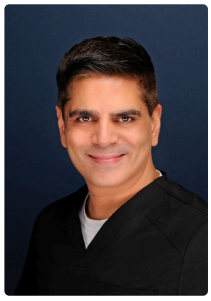

Abstract
Spinal Cord Stimulation (SCS) is an effective neuromodulator treatment for the management of chronic pain. Various SCS modalities with divergent mechanisms and therapeutic outcomes include traditional tonic stimulation, high-frequency (HF-10) stimulation, burst stimulation, dorsal root ganglion (DRG) stimulation, and closed-loop SCS. This review provides a comparative analysis of these SCS modalities, specifically in terms of their operating mechanisms, clinical efficacy, and specific indications. Standard SCS modulates pain pathways through continuous low-frequency stimulation, whereas HF-10 SCS acts independently of paresthesias and leads to neuronal desensmetization. By mimicking the natural patterns of neuronal firing, burst stimulation produces a stronger analgesic effect with less tendency for tolerance. DRG stimulation is intended for target pain treatment in localized pain syndroms. Because closed-loop SCS is the most technologically advanced method and personalizes stimulation in real time to be directed based of the elicited thresholds of evoked compound action potentials (ECAPs), it is likely to optimize therapy and result in superior long-term outcomes. A thorough understanding of these mechanisms and clinical outcomes is crucial for proper patient selection and improving treatment success. Further investigation is needed to finetune personalized SCS protocols and improve long-term outcomes.

History
Spinal cord stimulation is a device that is implanted and sends low levels of electrical impulses directly to the spinal cord to help relieve pain. This device debuted for practicians in 1967 and subsequently tried in humans by Dr. Norman Shealy and has advanced significantly since then. Although the first percutaneous lead was developed in 1975, major advances occurred in the 1980s with the introduction of multi-contact electrodes. The first commercially rechargeable system entered the market in 2004, the "High Frequency SCS" and "Burst SCS" were approved between 2014 and 2015, with the latest development being the "Closed-loop SCS." (1)

Description of the SCS (Spinal Cord Stimulation)
During spinal cord stimulation, two electrodes-containing leads inserted into the epidural space surrounding the spinal cord. These leads aim at spinal nerves that relay pain signals from a limb or torso to the brain. A battery pack or implantable pulse generator (IPG) is placed under the skin, commonly above the buttocks, with extension wires connecting to the spinal leads. The IPG emits electrical pulses for stimulating distinct nerve cells to reduce pain signals. The pulse configuration the stimulation waveform can be reprogrammed to change sensations and effects on the spinal cord. Traditional stimulation produces a tingling or pins-and-needles feeling known as paresthesia. (1)

Indications
New technologies have emerged in order to overcome these limitations; common indications of SCS include failed back surgery, refractory complex regional pain syndrome, diabetic peripheral neuropathy, axial low back pain, refractory angina pectoris, nerve-related pain, amyotrophic lateral sclerosis pain and post-amputation pain. (2)

Types of Stimulation
Ultra-high frequency stimulation (UHFSCS): This is a newer class of SCS that uses frequencies greater than 10,000 Hz, often around 20 kHz. UHFSCS has been shown to provide paresthesia-free pain relief by causing a deep depolarization blockade. A pilot study by Song et al. (2023) found that 83% of patients with axial low back pain experienced over 60% pain relief at 6-month follow-up with 20 kHz stimulation.

Closed-loop burst stimulation: An advanced modality combining the burst waveform with real-time ECAP feedback to adapt stimulation to physiological changes. This hybrid method may improve patient satisfaction and therapy durability. Preliminary data from the ECAP-BURST trial (2023, ongoing) support its use in reducing opioid dependency and enhancing pain control.

Conventional: Conventional spinal cord stimulation (tonic) - devices can provide impulses within a frequency range between 2 and 1200 Hz, with electrode placement determined according to the location of pain. (2)

High frequency: Traditional spinal cord stimulation elicits electrical impulses below the frequency of 1200 Hz, with the goal to mask pain perception by creating paresthesia. By contrast, HF10 stimulation is at a rate of 10,000 Hz, which better controls pain while avoiding paresthesia altogether. HF10 stimulation has shown to be effective for a wide spectrum of neuropathic pain conditions with a more targeted analgesic effect when compared to traditional treatment approaches. (2,3)

Burst: Derived from the natural bursting behavior of thalamic neurons, burst stimulation provides a paresthesia-free alternative to tonic stimulation. This helps in pain signaling reach until the thalamus and invokes paresthesia as well (tonic stimulation), which would not happen using burst stimulation, which is targeted at non-GABA receptors and works at the dorsal horn level of the spinal cord. The BurstDR (Abbott) is the most common and delivers a continuously current at 500Hz with 1 ms pulse widths over 10 ms, with bursts set 25 ms apart - leading to an interburst frequency of 40 Hz. (3,5)

DRG (Dorsal root ganglion): This technique is most beneficial for those patients who have had failure of conventional spinal cord stimulation or where paresthesia in a localized area, such as the groin, foot (lateral aspect), or in certain intercostal spaces is inadequate. (3)

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Closed Loop: This system measures Evoked Compound Action Potentials (ECAPs) from the spinal cord triggered by the stimulation pacing and uses the ECAPs to adjust the stimulation intensity in real time. This ECAP-controlled SCS approach maintains the level of the neural response (ECAP) at a pre-specified target by modulating the output of the STIM at 30 Hz (=1800 times/min), which compensates for changing distances between the epidural leads and the spinal cord. (4)

Neurophysiological mechanism of the SCS

Conventional: It does not require positioning of an electrode at the painful site with HF or burst stimulation. Instead, electrodes are placed high above pain to intercept pathways of pain signals and redirect pathways to higher levels of the nervous system. (1) Stimulation is applied with constant current or voltage settings followed by passive recharge. The stimulation is triggered by an implantable pulse generator (IPG) that may be rechargeable or not. This stimulation, when applied at high enough amplitudes, can elicit paresthesia, which can be different depending on the area of spinal cord targeted as well as individual neuroanatomical variability. (5)

High frequency: The exact mechanisms of action of high-frequency stimulation (HF SCS) are still not completely understood and have been elucidated in several theories including conduction block, inhibition of wide dynamic range neurons and interneurons, elevation of temperature, and modulation of glutamate uptake. HF SCS provides subthreshold stimulation to the patient. A proposed mechanism, termed "depolarization blockade," has been put forward in which HF stimulation establishes a reversible block to propagating action potentials. Another suggestion is that HF stimulation might induce neural desynchronization (decreased firing in lock step) among clusters of neurons. (4,5)

Burst: During burst stimulation, five 100 µs impulses are applied at 500 Hz frequency, with the duration of each impulse being 1 millisecond. Bursts have a frequency of 40 Hz and are followed by passive repolarization for about 5 ms until the next burst. The time period with no pulses, called the interburst interval, lasts 5 seconds. (3)

DRG (Dorsal Root Ganglion): The selective activation of A β, A δ, and C-fibers with low frequencies is one of the primary analgesic mechanisms of DRG stimulation. Through activation of the opioid receptor without the use of the GABA system, stimulation of the DRG at very low frequencies generates action potentials that serve to block pain stimuli. (3)

Closed loop: This system is believed to involve the inhibition of dorsal horn neurons that participate in processing pain sensation through the action of large-diameter dorsal column fibers on the dorsal horn by the action of inhibitory neurotransmitters (e.g. GABA). Additionally, patient movement changes the distance between the dorsal column fibers and electrodes, thus affecting the magnitude of the electric field and dose of stimulation. (4)

Comparation Between Types of Stimulation

Tonic vs High-frequency: This preference for elevated frequencies was clinically substantiated by Al-Kaisy et al. (8), who conducted a crossover study with a small cohort of patients diagnosed with failed back surgery syndrome (FBSS). Their results demonstrated that effective pain relief, measured through VAS scores, was attainable solely with stimulation at 5,882 Hz. Importantly, there was no observed dose-dependent pain relief between the 1,200 and 3,030 Hz frequencies, and a true high-frequency waveform of 10 kHz was not explored. In contrast, the PROCO study led by Thomson et al. (9) evaluated the impacts of various frequencies ranging from 1 kHz to 10 kHz in a sample of 20 participants, indicating that all assessed frequencies provided similar analgesic benefits.

A review of these studies revealed that all three demonstrated significant pain reduction with high-frequency (HF) waveforms compared to baseline levels, confirming the non-inferiority of HF waveforms against tonic stimulation. Caporal et al. (10) extended the findings of the SENZA study for involving the largest participant group and the most extended follow-up period, highlighting a clear advantage of HF over tonic stimulation in relieving both back and leg pain. Conversely, the studies by Bolash et al. (11) and De Andres et al. (12) did not provide conclusive evidence for the superiority of HF waveforms.

High-frequency vs Burst: There is a lack of sufficient evidence assessing the effectiveness of burst versus HF waveforms in the treatment of chronic low back pain (LBP). The studies conducted by Kinfe et al. (13) and Muhammad et al. (14) involved comparisons between burst and HF waveforms within the same limited group of patients suffering from failed back surgery syndrome (FBSS) with a primary complain of back pain. Both studies concluded that neither waveform demonstrated significant superiority in alleviating back pain; however, they did ascertain that burst stimulation was more effective than HF stimulation in diminishing leg pain at the 3- and 12-month follow ups.

Effects of Burst vs Tonic SCS: Given the distinct mechanistic differences, there are also variations in clinical outcomes. The meta-analysis, which aggregated data from 268 patients across five studies, indicated that burst stimulation had a greater analgesic effect compared to tonic stimulation (7). Specifically, burst stimulation resulted in a mean score reduction of 1.64, demonstrating its advantage over tonic stimulation. It is important to note that the 2013 study by De Ridder et al (15) was excluded from the meta-analysis due to difficulties in extracting variance and deviation data related to pain sources. Among the studies that were included, the superiority of burst stimulation was clearly established. Furthermore, the SUNBURST trial showed that patients preferred burst stimulation over the tonic waveform.(16)

Comparative Table of Spinal Cord Stimulation (SCS) Modalities

Modality	Frequency	Mechanism of Action	Clinical Use Case
Tonic SCS	2-1200 Hz	Paresthesia via dorsal column stimulation	General chronic pain, FBSS
High-Frequency (HF 10)	10,000 Hz	Sub-threshold depolarization block, desynchronization	Widespread neuropathic pain without paresthesia
Burst Stimulation	500 Hz bursts (40 Hz interburst)	Targets thalamic relay, paresthesia-free	Mixed back/limb pain with preference for non-paresthesia
Dorsal Root Ganglion (DRG)	~20-60 Hz	Targeted Aβ/δ/C fiber inhibition, opioid-mediated	Localized pain (e.g., CRPS, groin, foot)
Closed-Loop SCS	30 Hz (adaptive)	ECAP feedback adjusts stimulation in real time	Variable activity levels, postural pain changes

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Types of SCS (Spinal Cord Stimulation): A Comparative Analysis of Efficacy and Mechanism

Continued...

Comparative Table of Spinal Cord Stimulation (SCS) Modalities - Continued

Modality	Frequency	Mechanism of Action	Clinical Use Case
Ultra-High Frequency SCS	>10,000 Hz (e.g., 20 kHz)	Deep conduction block, potential glial modulation	Refractory axial back pain, future-proof option
Closed-Loop Burst	500 Hz burst (adaptive)	Dynamic burst delivery adjusted via ECAP feedback	Advanced adaptable therapy for refractory cases

Conclusion

Additional advanced modalities, such as ultra-high frequency SCS (UHFSCS) and closed-loop burst stimulation, have shown early clinical promise and warrant further investigation. UHFSCS provides deep paresthesia-free analgesia and may be optimal for certain neuropathic pain syndromes, while closed-loop burst technology blends the benefits of burst and adaptive feedback control for dynamic personalization. These developments mark a shift towards precision neuromodulation, demanding future studies comparing long-term outcomes and cost-effectiveness across all SCS types.

Key Findings Comparing Different SCS Waveforms Several studies have also shown high-frequency (HF) stimulation to be associated with improved pain reduction, versus baseline, and demonstrated non-inferiority versus tonic stimulation. The study by Al-Kaisy et al. was stimulation at 5,882 Hz while PROCO study results suggested similar analgesic effects of the frequencies spanning from 1 kHz to 10 kHz. Moreover, HF stimulation demonstrated definitive benefits when compared with tonic stimulation for back and leg pain in the SENZA trial, although several articles, including those by Bolash et al. of Cavalcante et al. and De Andres et al. was incapable of definitively demonstrating superiority of HF.

There was moderate evidence for recommending burst and HF waveforms over one another for chronic low back pain. Burst stimulation, however, was more effective in the reduction of leg pain.

Lastly, regarding burst vs tonic stimulation used in the same patient, a significant enhancement of analgesia was reported for burst stimulation over tonic hydrosimulation, and this is also evidenced in the SUNBURST trial where patients overall preferred burst stimulation over tonic stimulation. In summary, there is promising evidence of efficacy for HF and burst stimulation, but more studies are needed to conclusively determine the best performing waveform for different pain pathologies.

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Sertraline-Induced Riboflavin-Response Lipid Storage Myopathy: Report of Two Cases

Mustafa Almusawi, MD; Abdulwahhab Alhabib, MD; Aziz Shaibani, MD

Abstract

Lipid storage myopathies are a group of rare disorders characterized by abnormal lipid accumulation in muscle fibers, often leading to proximal muscle weakness and elevated creatine kinase (CK) levels. While genetic mutations affecting riboflavin metabolism have been implicated in some cases, riboflavin therapy has shown efficacy even in genetically negative cases (1). Sertraline has been reported in associated with lipid storage disease, specifically with Multiple Acyl-Coenzyme A Dehydrogenase Deficiency (MADD) (2). This report highlights two adult-onset cases of lipid storage myopathy due to MADD associated with sertraline therapy that responded favorably to riboflavin supplementation even before discontinuation of Sertraline. The Level of acylcarnitine returned to normal within 6 months of therapy.

Introduction

Lipid storage myopathies (LSM) are often linked to metabolic dysfunctions involving mitochondrial respiratory chains. Sertraline, a selective serotonin reuptake inhibitor (SSRI), has been associated with mitochondrial dysfunction, including disruption of respiratory chain complexes (3). While the link between sertraline and lipid storage diseases is not fully understood, several case reports suggest a potential role. Furthermore, riboflavin therapy has emerged as a promising treatment modality, even in the absence of detectable genetic mutations in riboflavin-related enzymes. We present two cases of sertraline-induced lipid storage myopathy due to MADD, emphasizing the therapeutic benefit of riboflavin and the potential interaction between sertraline and the riboflavin metabolic pathways.

Case Reports

Case 1: A 63-year-old female presented with a six-month history of progressive proximal muscle weakness, predominantly affecting the lower limbs. Laboratory investigations revealed elevated CK levels (700 U/L) and a myopathic pattern on electromyography (EMG). Muscle biopsy showed lipid deposition confined to type 1 fibers, consistent with lipid storage myopathy (Figures 1 and 2). The patient had been on sertraline therapy for depression for two years. Genetic testing for Electron transfer Flavoprotein (ETFA, ETFB, and ETF-DH genes) and the other metabolic enzymes was negative including CPT-2 gene. Whole exome sequencing revealed no pathogenic mutations. Total and free serum Carnitine was normal. Acylcarnitine analysis revealed significant elevation of multiple length fatty acid chains consistent with multiple acyl-Coenzyme A dehydrogenase deficiency (MADD) (Figure 3) Riboflavin supplementation (100 mg/day) was initiated, leading to significant clinical improvement and normalization of CK levels within six weeks and acylcarnitines level within 6 months. Despite continued sertraline use, the patient's symptoms resolved, suggesting a potential compensatory effect of riboflavin therapy.

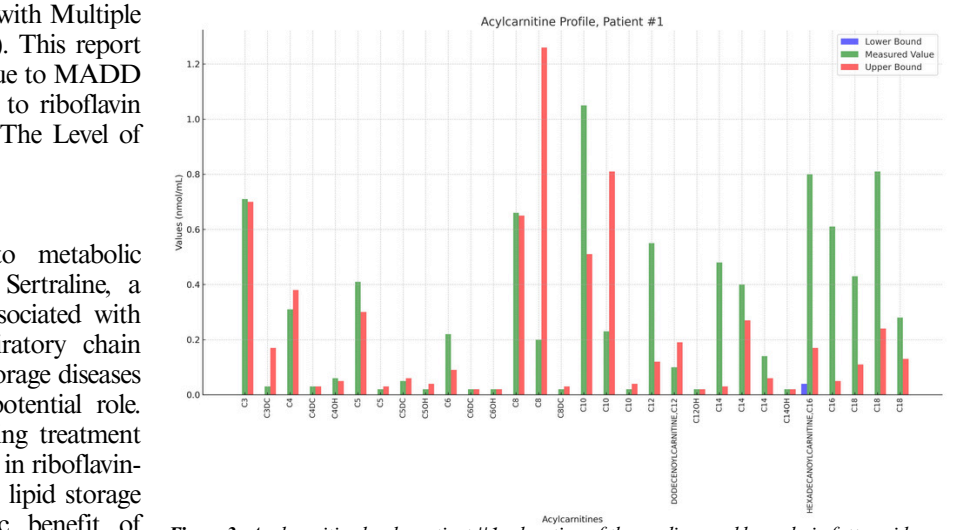

Figure 3: *Acylcarnitine levels, patient #1: elevation of the medium and long chain fatty acids.*

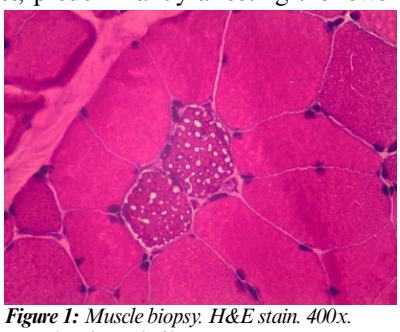

Figure 1: *Muscle biopsy. H&E stain. 400x. vacuolated muscle fibers*

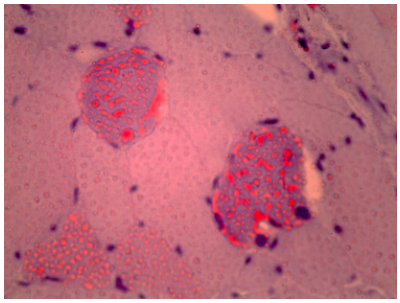

Figure 2: *Muscle biopsy. Oil red O (ORO) stain. 400x. The contents of the vacuoles stained positive indicated lipid contents in type 1 fibers.*

Case 2: A 64-year-old female with a six-month history of proximal muscle weakness and fatigue was referred for evaluation. CK levels were elevated (1000 U/L), and EMG showed myopathic changes. Muscle biopsy revealed lipid accumulation in type 1 fibers (Figure 4). She has been on sertraline for generalized anxiety disorder for three years. Genetic testing was negative for the metabolic myopathy including ETFs and CPT2 genes. Whole exome sequencing revealed not pathogenic mutations. Total and free serum. Carnitine was normal. Acylcarnitine analysis revealed significant elevation of multiple length fatty acid chains consistent with multiple acyl-Coenzyme A dehydrogenase deficiency (MADD) (Figure 5). Riboflavin therapy (100 mg/day) was initiated, resulting in marked improvement in muscle strength and reduction of CK levels within eight weeks. Like Case 1, the patient's symptoms improved despite ongoing sertraline therapy. In both cases Sertraline was discontinued 2 months later once the treating physician learned about a possible association. The CK and the levels of the fatty acid chains normalized 3 months later (Figure 6).

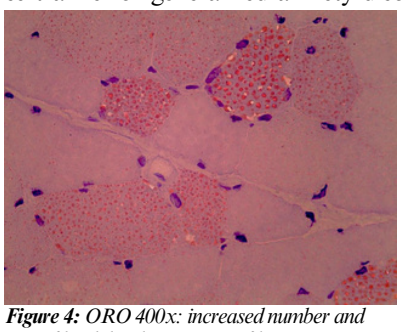

Figure 4: *ORO 400x: increased number and size of lipid droplets in type 2 fibers*

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Sertraline-Induced Riboflavin-Responsive Lipid Storage Myopathy: Report of Two Cases

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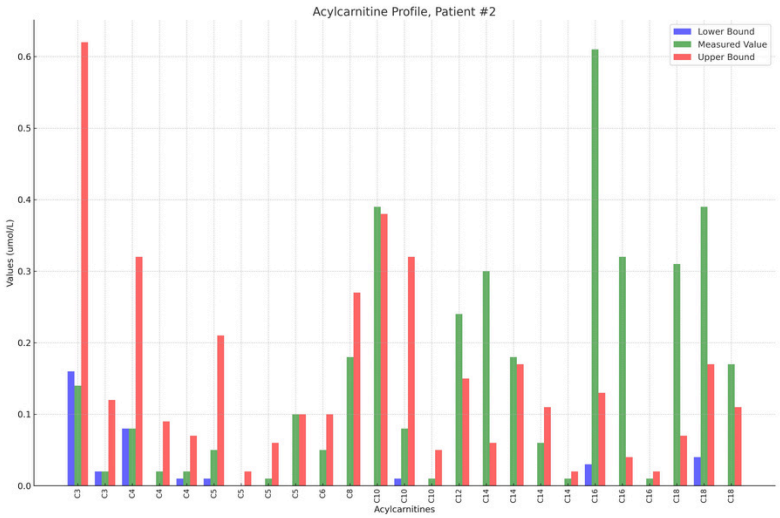

Figure 5: *Acylcarnitine levels, patient #2: elevation of the medium and long chain fatty acids typical for multiple acyl Coenzyme A dehydrogenase deficiency (MADD).*

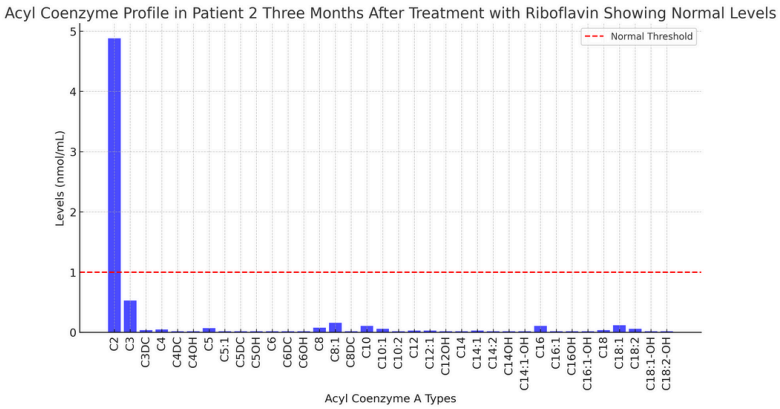

Figure 6: *Acylcarnitine levels, patient #2: normalized values.*

Discussion

These cases underscore the potential role of sertraline in disrupting mitochondrial function, in particular the electron transfer flavoproteins which are essential for the integrity of the mitochondrial complexes. Electronic transfer abnormality leads to impaired fatty acid oxidation and thus leading to lipid storage myopathy. Sertraline's interference with riboflavin-dependent enzymatic pathways may explain the observed lipid accumulation and muscle dysfunction. There are several case reports of MADD in association with Sertraline therapy. Riboflavin, a key cofactor in mitochondrial respiratory chain complexes, appears to counteract this disruption, restoring metabolic homeostasis even in the presence of sertraline.

The absence of genetic mutations in these cases highlights the need for broader diagnostic criteria and therapeutic considerations for LSM. Riboflavin therapy should be considered in cases of lipid storage myopathy, particularly when associated with sertraline or other SSRIs. Furthermore, these findings warrant increased awareness among psychiatrists regarding potential adverse effects of SSRIs on muscle metabolism and the importance of early intervention. Preventive use of Riboflavin with chronic Sertraline therapy is to be considered.

Conclusion

We report for the first time two cases of adult-onset sertraline-induced lipid storage myopathy that responded favorably to riboflavin therapy clinically and serologically. These cases suggest that sertraline may interfere with riboflavin metabolism, leading to mitochondrial dysfunction and lipid accumulation in muscle fibers. Riboflavin supplementation offers a safe and effective treatment option, even in the absence of genetic abnormalities. Discontinuation of Sertraline is reasonably warranted. This report also emphasizes the importance of muscle biopsy in revealed treatable lipid storage myopathy in elderly patients with progressive myopathy of unidentifiable cause (4). Further research is needed to elucidate the mechanisms underlying SSRI-induced myopathies and the role of riboflavin in their management. It is reasonable to recommend preventive riboflavin therapy in patient administering Sertraline.

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Happy Friday Highlights

Hello Colleagues! By way of introduction, I started sending out an email post on Fridays right after COVID closed everything down in April 2020. My initial posts were just a few sentences long, were sent to a few people, and they included a link to a funny COVID parody song. One thing led to another, the posts got a little longer, the readership got wider, and the music and topics more varied. My initial thought was to write until the pandemic was declared over. I never dreamed that I would still be hunkered down every Thursday night writing a post five years later! I learn something every week. Randy Evans suggested that I sent some to Broca's so here are a couple for your reading pleasure. My topics are usually not medical, but these two have a medical flavor to them that I thought you would find interesting.

Deborah Friedman, MD, MPH
Yellow Rose Headache and Neuro-Ophthalmology, Dallas

March 14, 2025

I hope you are doing well and that you had a great week! While driving home from the gym last Sunday I listened to a program on the classical music station (WRR) showcasing teens who have excelled musically called "From the Top." I have heard it before - these young musicians are all amazingly talented. The host, Peter Dugan, introduced Noah Carver who, from the speaking voice, sounded female to me (as in Noa). Then Carver began to sing and I realized I was listening to a tenor, which didn't quite fit my presumption based on the speaking voice. Noah is indeed male (as it turns out, the interview was from 2022 and his voice has changed) and he sang beautifully. Dugan asked more questions after the performance when Noah revealed that he had been blind since birth.

Noah grew up on Beals Island Maine where his father, who loves the outdoors and the ocean, is a lobster fisher. Noah related that his parents found out that he was completely blind from Leber's Congenital Amaurosis when he was 8 months old and made the decision to raise him in such a way that he would learn and enjoy everything that sighted children were able to do. When his mother realized that his school was no equipped to teach him, she did it herself, helping him learn concepts at their kitchen table that are typically learned visually.

Dugan asked how he learned his repertoire and Noah replied that he first learned vocal music from listening to it, imitating what he heard on records. He later incorporated braille music. As a neuro-ophthalmologist (albeit not an ophthalmologist) this was news to me - I never knew that there was braille for music. Noah explained that Louis Braille developed it in addition to the literary system. Braille (pronounced "bray") was a French educator who lived in the first half of the 19th century. He was blinded in one eye at age 3 in an accident. Despite treatment, the eye became infected, which spread to the other eye ("sympathetic ophthalmia"), resulting in total blindness. Braille was a good student and got a scholarship to attend the Royal Institute for Blind Youth, which is where he started working on braille. At the time, the founder of the school, Valentin Haüy (a sighted philanthropist), created books for the blind using embossed heavy paper and Latin letters. Because the reading process was so slow, the text tended to be sparse, and it did not help children learn to write. Braille developed a tactile system using a 6-position cell of raised dots (2 dots wide, 3 dots high) called "decapoint" to allow blind people to read and write efficiently and quickly. His system remains essentially unchanged to this day.

Braille also had a musical ear and became an accomplished cellist and organist. After his career as a professor at the Institute teaching history, geometry and algebra, he played organ for churches all over France. He published his first book of braille musical notation in 1829 which used the raised method of Haüy. The final version used the same 6-position cell as literary braille.

Although almost any printed music can be written in braille, the notation is different. It assigns a braille letter to each note, starting with the note C (written "d") and progressing through the keyboard and alphabet from there (B is "j"). The pitch of the note using positions 1, 2, 4, and 5 in the cell and additional dot combinations in positions 3 and 6 are added to indicate the length of the note (i.e., quarter note, half note, etc.). There are also braille "accidentals" (sharp, flat, natural), bar and octave symbols, markings to indicate loudness and speed (e.g., diminuendo, crescendo, ritardando, staccato), fingering, repetition symbols, chords and every other musical notation you can imagine. Braille music can be transcribe by professionals and is now also done by computer.

An article about Noah Carver revealed that he started taking professional voice lessons when he was in high school and studied opera with Gary Magby. He won a $10,000 prize from the Jack Kent Cook Foundation and is currently a student of Vocal Performance at the Eastman School of Music in Rochester, New York. Besides his music and schoolwork, Noah downhill skis with the help of a guide skiing behind him to transmit information about the terrain ahead via earphones. He also enjoys horseback rising, hiking, playing clarinet and piano, running cross country, lobster fishing with his father and training volunteer ski guides.

In his radio interview, Noah expressed immense gratitude for his parents for their support and encouragement. He got emotional and so did I. So inspiring! The human spirit is truly a powerful thing!

Have a creative and enjoyable weekend!

Deb

https://www.youtube.com/watch?v=b9mbtFh4gqE

Bonus: Story about Noah from a Maine TV station
https://www.youtube.com/watch?v=30SFpkwosjM

January 17, 2025

Happy Friday!

I sure hope that you had a good week! Lots of famous people are celebrating their birthdays today including Benjamin Franklin (subject of a previous Happy Friday), Al Capon (never sit in a restaurant with your back to the door), Betty White (Golden Girl!) and Muhammad Ali (float like a butterfly, sting like a bee). Today also marks the beginning of prohibition in the U.S. in 1920 and, probably not coincidentally, is National Bootleggers Day. The U.S. bought the Virgin Islands from Denmark for $25 million in on January 17, 1917 - perhaps another land deal with Denmark is on the horizon?

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Happy Friday Highlights

Continued...

This is going to be an unusual post... today marks the anniversary of the death of brothers Chang and Eng Bunker. Who were they and how did they manage to die on the same day? Chang and Eng were born in the Meklong Village of Thailand (known then as Siam) in 1811. They were conjoined twins - joined at the sternum by a flexible band of ligament and cartilage which connected their livers. Their fame generated the expression "Siamese twins" to describe conjoined twins and they were "two of the nineteenth century's most studied human beings."

Their father died when the twins were young, possibly of smallpox. Their mother, Nak, raised them like her other children without any special attention and they were lively boys, running and playing with other children. They were "discovered" by Scottish merchant Robert Hunter in 1924. Hunter was a trade associated for the Siamese government who traveled freely throughout Siam. He reportedly spotted the twins swimming in the Menam River while he was on a fishing boat, at first mistaking them for a "strange animal." He saw the economic opportunity of bringing them to the West to exhibit them, which took five years to accomplish. They were supposed to tour for five years and then return to Siam - and their mother gave them up for dead after 15 years - but they were very much alive.

Hunter brought Chang and Eng to the U.S. by boat in 1829, at age 17, accompanied by a Siamese translator. Their arrival in Boston was reported in the newspapers (with racial stereotypes and falsehoods) and they were inspected by numerous physicians. They toured the British Isles and returned to New York in 1831, much more proficient in English. Basically, their manager charged people to see the "boy" running, doing somersaults, swimming, playing checkers, and doing parlor trickers. They were promoted ass being "exotic," wearing their hair in pigtails and dressed in "oriental" clothing. There were a few incidents along the way, one in Lynnfield, Massachusetts when they were harassed by locals while hunting game (they struck one of the harassers with the butt of a gun and then fired at him; fortunately, the gun was blank). The second was in Alabama when a surgeon asked to inspect the area at which they were joined. When the twins refused, he accused them of being imposters.

They left their manager in 1832 and toured independently as "The Siamese Twins," speaking English, answering questions from the audience, wearing American clothes and presenting themselves as men rather than boys. They toured on and off in the US and abroad until 1839, when they moved to North Carolina to enjoy hunting and fishing away from the crowds, purchasing 150 acres for $300 in the mountains. They also became naturalized U.S. citizens (despite a federal law limiting citizenship to whites). The twins were quite well-off financially from touring, and their property was the third-most valuable in the country in the early 1840s.

The local newspaper published an article about the twins' intention to marry - and they did - to sisters Sarah and Adelaide Yates. There was a lot of public criticism about the marriages because of their race, not the fact that they were conjoined. They took the last name Bunker in honor of a woman they met and admired in New York.

The twins became quite wealthy, bought a second home, and liver in luxury as plantation owners (yes, with slaves). The plantations grew food and raised animals with no tobacco crops.

They also had children, lots of them. They managed by alternating houses every few days and the twin who owned the house would do what he wanted while the other went along and kept quiet.

They toured again in the late 1840s to support their then-7 children, mingling with audiences and speaking about their lives, marriages and politics, displaying their wit. They signed with P.T. Barnum but did not get along with him, so the contract lasted only a year. After touring in California, they returned to North Carolina at the start of the Civil War. Newspapers reported fake news (it's not a new thing) about them being divided over the issue of slavery, charging that Chang wanted the ligament connecting them to be painted black but Eng opposing it (they had different personalities but did not disagree on the issue). That is, Chang wanted their Union "dissolved" while "Dr. Lincoln" said that surgery would be "dangerous for both parties." They became symbols of the American Union.

After the Civil War, their slaves were emancipated and they toured again, presenting themselves as old men with lots of children, including sons who were injured in the war. They also toured internationally. In all, they had 21 children and 1500 descendants as of 2006.

Chang was paralyzed after a stroke in 1870 and began drinking heavily. He died in his sleep after a bout of bronchitis. When Eng's son woke him up announcing the news, Eng said "Then I am going." And he did. They lived for 62 years, the longest lifespan of conjoined twins until 2012. Today, they could have easily been separated surgically, although it would have been fatal when they were young. William Pancoast (of lung tumor fame) did the autopsies. Chang died of a blood clot in the brain and Eng "died of fright," or perhaps blood loss as his circulation pumped blood into his dead brother's body and got none back in return. Books, movies and musicals have been made about them.

Conjoined twins occur in 1 in 50,000 to 1 in 100,000 births. About half are stillborn and an additional third die within 24 hours. Females are three times as likely to born alive than males. There are many types of conjoined twins, depending on which body parts are joined and which are separate. The first successful separation of conjoined twins was in 1689; the first successful separation of twins joined at the head was in 1955, although the smaller twin was impaired. Many other difficult and technical surgical separations have been performed since then, with variable success.

Was that different enough for a Friday read? It was my pleasure. Have a great week!

Deb

https://www.youtube.com/watch?v=PDSSGyPurmE

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CONGRATULATIONS!

2025 Resident Poster Competition Winners!

1st Place

Exploring Cross-Disease Relationships of Adult and Childhood Neurological Disorders in Texas and Nationwide: Insights from All of Us. Study and DSoHS

Hyunyong Koh, MD
Baylor College of Medicine

2nd Place

Safety of Thrombolytic Therapy in Acute Ischemic Stroke Patients with History of Abdominal Aortic Aneurysm Repair: A Retrospective Study

Pichatorn Suppakitjanusant, MD
Texas Tech University Health Sciences Center

3rd Place

Assessing Mortality and Safety of IV Thrombolysis in Ischemic Stroke Patients on Direct Oral Anticoagulants (DOACs): A Systematic Review and Meta-Analysis

Abayz Asmar, MD
Houston Methodist

STAY CONNECTED

on all things TNS!

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In Rememberance

Dr. Alexander R. Lim

February 20, 1942 - December 31, 2024

TNS President, 1989-1990

View Obituary

Dr. Shirley Molenich

TNS President, 1988-1989

A longtime Fort Worth neurologist, Dr. Shirley Molenich was admired for her compassion, advocacy, and leadership. She pioneered efforts to support hearing-impaired patients and remained active in medical organizations until recent years. Her dedication and friendship will be remembered by all who knew her.

BUSINESS OF NEUROLOGY VIDEO SERIES

2025 Videos Include:
Corporate Practice of Medicine Overview and Why Get Involved in Organized Medicine

Need help with Coding?
Employing APPs?
How about Contract Negotiations?
Enhancing your Practice with Ancillary Services?

Congratulations

Lifetime Achievement Award Recipient

Kimberly E. Monday, MD

Dr. Monday is a former TNS president, an educator, and an outstanding neurologist. We are so proud to honor Dr. Monday and thankful for her commitment to the TNS and field of Neurology.

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TNS COMMITTEES

Membership Committee

Join this committee and bring awareness of TNS to Texas Neurologists and those in surrounding states and countries. Encourage APPs (and other allied health professionals) to join TNS and work with other committees to engage current membership. Review, approve, and recommend pending members to the board for approval.

Medical Economics Committee

This committee serves as a forum to discuss topics encountered in everyday practices. Bring your concerns and/or accomplish-ments to the group. Assist in the brainstorming of topics for the "Business of Neurology" video series. Help TNS help its membership.

Education Committee

TNS has two successful conferences each year and it starts with this committee. Committee members along with each conference program director(s) help create agendas for the TNS annual meeting and summer conference. Potential topics and speakers are discussed. This committee is mainly focused on providing the TNS membership with high quality education and CME.

APP Committee

Create a forum for APPs and answer the question "what can TNS do for you?" Through the committee, build relationships with other APPs around the state and provide support in areas of need - resources, content, networking.

Communications Commitee

Outreach is important! This committee works to develop materials/projects as they relate to TNS; grab the attention of the current and future membership using its social media platforms and bi-annual newsletter and increase neurology aware-ness.

Independent Practice Committee

Calling all independent practice physicians! Identify and cultivate a relationship of those in independent neurological pract-ices around the state and determine ways TNS can help. Help create/host discussions, content, resources, or provide your view-point to others.

Legislative Committee

More of how we practice neurology is determined at the Texas Capital and in D.C. during a legislative session. This committee fosters with legislators and policy makers to educate them about the delivery of neurologic healthcare to all Texans.

Women Neurologist Section

This section gets together during TNS conference to meet fellow TNS women neurologists and share experiences. Some cities have created their own "chapter" to establish networking on a grassroots level. Don't miss out. Get involved TODAY!

Awards and Nominations Committee

Be apart of this committee and help showcase TNS by creating awards and honoring those that are not only outstanding in the field of neurology but members of TNS. Help the board determine the next leaders to serve on the board.

Grants Committee

TNS gives back through the grants committee. Annually, committee members review submitted applications to determine which one/ones achieve the goal of improving and supporting neurological practices, education, and disease awareness and prevention. Continuing to further neurology is what this committee is designed to do.

Resident and Medical Student Committee

Resident representatives from all the Texas programs in addition to TNS members work to develop projects or materials geared toward neurology residents. This committee is also responsible for the continuing development of the "Business of Medicine" program and TNS related resident educational programs. This committee also includes medical students as they venture into neurological residency.

For more information, visit the **TNS Website.**