TEXAS NEUROLOGICAL SOCIETY SUMMER 2019

Broca's Area

The Voice of Texas Neurology

President's Message
New Medical Marijuana Legislation

The 140 days of the Texas Legislature was eventful as always this past term. A large number of bills had potential impact on the field of neurology, and a few survived to arrive on Governor Abbot's desk for signature. Those that died in committee or were significantly changed included ones regarding end-of-life issues, scope of practice challenges, and the use of antipsychotics in nursing homes and other facilities. The TNS followed these bills carefully and made certain through the TMA and other agencies that our voices were heard. Bills regarding balanced billing and regulation of short-term non-ACA compliant insurances were compromises that serve the public.

The legislation that garnered the most attention was the plethora of bills regarding hemp and cannabis. Hemp farming was legalized on a federal and state level, so CBD oil will be even more plentiful, and will certainly be used by a number of our patients with or without our support. No changes were made on the criminal production, distribution, possession, or use of non-medical marijuana, but there was a critical change made in the medical use of low-THC cannabis. Pending signature by the governor, on September 1, 2019, board-certified physicians will be able to prescribe medical marijuana from a licensed dispensary. The approved indications will include "epilepsy, a seizure disorder, Multiple Sclerosis, spasticity, amyotrophic lateral sclerosis, autism, terminal cancer, or an incurable neurodegenerative disease."

A number of questions would be appropriate to ask at this point. The approval for seizures was extremely narrow in 2015, and has been used by very few patients and prescribed by even fewer neurologists. As of September 1, though, every board-certified neurologist with a Texas license can prescribe for any of these conditions, as long as he or she "dedicates a significant portion of clinical practice to the evaluation and treatment of the patient's particular medical condition." This wording is very important to all neurologists, as there is no definition within the bill or within the TNS as to what a "significant portion" would entail.

Using MS as an example because that is my specialization, the question as to whether general neurologists would be able to prescribe it has been answered in the discussion of the bill throughout its original filing through to its final amendment and passage. The answer has been yes, as it is clearly within the scope of practice of neurology to treat this condition. Similarly, epilepsy, spasticity, and ALS are well within the training of neurologists. The more ambiguous conditions, then, are autism, terminal cancer, or an incurable neurodegenerative disease. Autism and terminal cancer can be treated by a number of non-neurologic specialists, of course. The type of conditions considered "neurodegenerative" is also not clearly spelled out, and could arguably include painful conditions such as peripheral neuropathy, myopathy, and complex regional pain syndrome, as well as non-operable degenerative disc disease. Currently, it would appear that the Texas Medical Board would be the only authority on whether use of cannabinoids for these conditions goes beyond the scope of the legislation, and it is unlikely that there will be any more stringent oversight.

Edward Fox, MD, PhD

Neurologists will need to register with the state in order to prescribe medical marijuana. The compassionate use registry already exists, and is easy to join. Interestingly, the new legislation specifically states "the department may not publish the name of a physician registered under this section unless permission is expressly granted by the physician." In other words, participation does not put one on a "list" that could be used by patients to shop for prescribers, and could not be used for singling out prescribers for outside review.

Continued on page 3

CONTENTS

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Editor's Notes

Randolph W. Evans, MD

I thank our officers and other contributors for their excellent submissions to this issue. We look forward to seeing you at the 16nd Annual TNS Summer Conference at the Marriott Marquis Houston. Sara Westgate, program director and the education committee have planned an excellent program.

THE FIRST UNITED STATES OPIATE CRISIS

Opiate addiction has become increasingly prevalent in the United States with a horrific increase in the number of overdoses from about 8000 in 1999 to over 50,000. Tragically, this is the second U.S. opiate crisis (Hager T. Ten Drugs . How plants, powders, and pills have shaped the history of medicine. Abrams press, 2019).

Opium was well known in the early days of the Republic. Thomas Jefferson took laudanum (a tincture of opium) to help him maintain his "habitual state." Opium became increasingly used for any type of physical discomfort and depression. Opium addiction was recognized by 1840 but was felt to be a benign habit compared to alcoholism. "Liquor generally arouses the animal, while opium subdues this completely. Indeed, in its place it awakens the diviner part of human nature and can bring into full activity all the nobler emotions of the human heart (New York Times, 15 March, 1840, p 132)."

Advances in Europe would fuel the first U.S. crisis. In 1806, the German pharmacist, Serturner, isolated an alkaloid from opium. In tests on himself, he became addicted and wrote in 1812, "I consider it my duty to attract attention to the terrible effects of this new substance I call morphium [after Morpheus, the Greek god of dreams] in order that calamity be averted." Codeine was synthesized in 1832. In 1895, Bayer pharmaceutical introduced heroin (the name came from the German "heroisch" which means heroic, strong from the ancient Greek word "heros") which was marketed for children with coughing and colds and as a morphine substitute.

Merck Pharmaceutical became expert at producing large quantities of morphine as morphine replaced opium in medical use. However, it had to be taken po or by suppository with slow onset and variable results.

In 1853, the French surgeon, Charles Gabriel Pravaz was trying to find a way to treat arterial aneurysms by direct injection. He had a local metalworker make a hollow needle out of platinum to which he attached a small

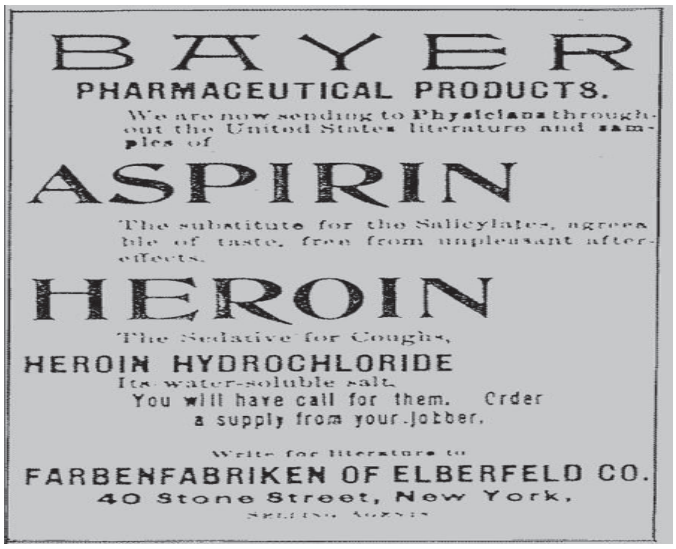
silver plunger: the first syringe. The same year, Scottish physician, Alexander Wood, invented a similar syringe and was the first to use injectable morphine as "A New Method for Treating Neuralgia by the Direct Application of Opiates to Painful Points". At first it was thought injecting lower measured doses of morphine would treat opium addicts but addicts got a bigger, faster rush and there was more risk of addiction.

WOOD'S SYRINGE

During the Civil War, morphine was ubiquitous for treatment of wounds, dysentery, and malaria. In the North and the South, people grew poppy flowers in their home gardens to be processed into morphine. Long after the war ended, numerous veterans with ongoing pain were taught to self-inject morphine. The increasing number of addicts was called "the army disease."

During the 1870s and 1880s, per capita use of opiates tripled. Morphine and syringes were sold over the counter at drugstores and by mail order. In the 1890s, the Sears & Roebuck catalogue offered 2 vials of Bayer Heroin, a syringe, and 2 needles for $1.50.

America's first opiate epidemic was called "morphinism" by the medical community. In 1912, Bishop wrote, "Every physician is familiar with at least a few cases of morphinism. Nearly every physician has made effort to rescue from the addiction its victim, and as a rule has given over the effort as hopeless, because even when the patient has been taken off his drug, he relapsed, or while under treatment he did not have the courage to persevere or the stamina to endure the necessary suffering. The profession as a whole has adopted a cynical attitude toward the possibility of permanent cure and many have relegated to quacks and charlatans the treatment which these poor people seek (Bishop ES. Morphinism and its treatment. JAMA 1912;LVIII:1499-1504)."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Other than veterans, by the 1880s, morphine addicts were mostly middle and upper class, professionals, and business people who were taught by their physicians to self-inject for pain. It was estimated that in 1885, up to 1/3 of physicians in New York were addicts. Alcohol and tobacco were considered men's drugs and the majority of users of laudanum and morphine were women being treated for menstrual cramps, hysteria (any psychological problem of women), and melancholia (depression). By the late 1800s, up to 4.59 per 1000 people were addicted to opiates

By 1860, opium and morphine were suspected to be responsible for 1/3 of all poisonings in the U.S. By the late 1800s, morphine was the most popular method of suicide for women and 2nd for men after guns. Morphine was also a popular and virtually undetectable way of killing people as the first good test for detection of morphine was not developed until the 1930s.

New laws and regulations decreased the use of opiates (Courtwright DT. Preventing and treating narcotic addiction-a century of federal drug control. New Engl J Med 2015:373:2095-2097; Nevius J. The strange history of opiates in America: from morphine for kids to heroin for soldiers. The Guardian). The Pure Food and Drugs Act of 1906 required labeling of patent medicines containing opiates, cocaine, alcohol, and cannabis. Between 1895 and 1915, opiates were no longer available without a prescription due to new state laws. In 1909, Congress passed a law banning the importation of opium and criminalizing possession. The Harrison Narcotic Act of 1914 led to near-prohibition of medical opium as the law was interpreted that a doctor could not prescribe opiates to an addict. Physicians were arrested and some were imprisoned.

President's Message *(cont.)*

One confusion about medical marijuana is regarding the actual product. The only product approved is low-THC, defined as 0.5%. CBD must be present with at least a 20:1 ration to THC, and this makes the medication minimally psychoactive. It was not approved for use other than in a liquid form that is not to be mixed into food, just taken orally in a prescribed volume. Up to 12 dispensaries in the state are allowed, and at the time of this writing, no set starting dose or advice can be given for any individual condition. However, on September 1, it is likely that the dispensaries will provide more information for everyone, and as with many symptomatic medications, we will have to make our own algorithms for treatment.

Conditions discussed but not specifically named as indications include PTSD and chronic pain. The reservations by the legislators who argued against inclusion revolved around the subjective nature of these conditions compared to the approved indications. "Slippery slope" arguments abounded, and as time grew short, there was a genuine sense of surprise that the bill was heard and passed in the senate. Receiving 100% support within the senate was the true shock, though. Why this occurred is complex, but it boils down to the combination of the tenacity of the authors and the extraordinary testimony of a number of people at the committee meeting level. The parents of children with neurologic conditions had the most impact by far, but adults with MS and other conditions were also very compelling. You could visibly see the change in attitude of some of the legislators to their emotional testimony.

I found it surprising that I was the only physician to ever testify on behalf of the bill. No oncologist, pediatrician, pain management physician, or psychiatrist spoke either for or against the legislation. As an advocacy volunteer for the National Multiple Sclerosis Society, I have been informed about similar state legislation for years, and had seen it approved in over 30 states before Texas, including all surrounding states. Working with the advocacy representatives for the NMSS and the TNS was a pleasure. Lobbyists are necessary for two reasons – to inform us of impending threats and opportunities, and to further our goals at our request. It is my pleasure to let you know that we have been well represented at the state level by our lobbyist Jim Dow. The TNS will continue to support the best interests of neurologists, and thanks its members for making legislative efforts possible.

Dr. Fox will be speaking more on this topic at the TNS Summer Conference on Saturday, July 27 at 12:30 p.m.

TNS Advocacy Report

BIPARTISANSHIP BREAKS OUT IN TEXAS LEGISLATURE!

Sara Austin, MD, Legislative Chair and Jim Dow, TNS Lobbyist

That "elections have consequences" has become a hackneyed cliché, around the internet and the Texas Capitol. But old sayings exist for real reasons, and with the 86th Session of the Texas Legislature behind us, what we know is this: the Texas Capitol saw a real return to bipartisanship in fact and in practice for most of 140 days.

House Bill 1—The Budget—passed with 1 vote against in both chambers. The most contentious big issue was Senate Bill 2—property tax reform (more like restraint and transparency)—passed with 48 votes against in both chambers; House Bill 3—school finance reform—passed unanimously through both chambers.

Maybe more telling is a look at what failed to pass: Democrats declared victory by killing the nomination of David Whitley to be Secretary of State, a statewide sales tax swap for property tax relief, increased penalties for ineligible voters, bans on certain abortions, and protections for Confederate monuments. Republicans won by killing their usual share of Democratic initiatives—which is to say a lot. But most notably lessened penalties for the possession of marijuana and death penalty reforms died especially high-profile deaths.

These successes and failures were no accidents. Twelve new Democrats in the House and two new ones in the Senate, swept into office by 2018's wave election, created real and predictable procedural roadblocks on the red meat social conservatives' agenda. And their existence from day one was recognized by both chambers' leaderships. This was most pronounced in the House where first time Speaker Dennis Bonnen created a body that looked like something Texas hasn't seen since the days of George W. Bush and Speaker Pete Laney. But we also saw a substantially kinder, gentler Lt. Governor Dan Patrick. Patrick publicly remained mostly true to form as movement conservative, but on the big issues he governed with some eye toward the practical realities of the new Legislature, often driving the car to the edge of the cliff, but ultimately backing up and parking it in the space called "workable compromise."

For both men, this happened with present and future in mind. The present dealt with the makeable and unmakeable compromises discussed above. The future was the real prize. Both leaders seemed reconciled to the fact that the 2020 election could look a lot like 2018's, but now with a lot less margin for error for Texas's long-ruling political class. For the first time in a decade, Republicans governed more with an eye toward the General Elections rather than their own primaries. Whether the far-Right will abide by this remains to be seen, but it's inarguable that 2019 saw Texas's Legislature take a hard turn toward the middle.

THE FIGHTS TNS FOUGHT

On several issues, Texas Neurologists found themselves front-and-center in a way they've never been before. Due to complicated interpersonal dynamics and some House v. Senate food fights, neurology had some surprising fights to fight. However, in a happy working partnership with the TMA, most of those fights were won.

MEDICAL MARIJUANA

Dr. Ed Fox played a leading role as the voice of Texas medicine in one of the most improbable wins of this session as HB 3703 was passed and is now sitting on Governor Abbott's desk. We fully expect that he'll sign it into law.

The bill removes the two-physician requirement for prescribing and expands the list of treatable conditions to include epilepsy (no longer specifically "intractable epilepsy"), spasticity, incurable neurodegenerative diseases, ALS, MS, seizure disorders, autism and terminal cancers. HB 3703 maintains Texas's current 0.5% THC limit, which is much lower THC than what's available in other states.

Maybe it's not the stuff of moon landings, but it was a giant victory for incrementalism. Looking forward, its passage makes clear that the Legislature is open to exploring the science of medical cannabis and dealing with the political realities attached thereto. TNS should expect and endeavor to remain a leading voice of science and medicine in this ongoing debate.

SCOPE OF PRACTICE

Chiropractors waged a pitched battle for their expanded scope of practice that would have included a definition of "neuromusculoskeletal system" in the Texas Occupations Code and allowed chiropractic treatment and diagnosis of the neuromusculoskeletal systems.

Their argument went that failure to act on their legislation would have resulted in a doomsday cascade of events; namely that chiropractic schools will close their doors around Texas and move out-of-state with chiropractors no longer being able to operate their businesses inside of Texas. This was primarily built around the premise that the pending litigation (about testing for vertigo) between TMA and Texas Chiropractic Board of Examiners would somehow wipe them out, which is a demonstrably false argument.

Dr. Sara Austin offered compelling committee testimony in opposition to this legislation, and through the work of both TMA and TNS, it ultimately failed to find its way to the floor of either chamber.

If the chiropractors' dire warnings turn out to have been false, and they remain in business two years from now advocating before the Legislature on more of the same ideas, TNS can expect another hard fight.

END OF LIFE/TREAT UNTIL TRANSFER

A key defensive stand came on SB 2089, which would have compelled physicians and hospitals to continue providing futile medical care to patients in a persistent vegetative state or other irremediable trauma until they can be safely transferred to another medical facility willing to treat them. If passed, this dangerous legislation would have further eroded the right of a physician to exercise their independent medical judgment or follow well-accepted norms of medical ethics when treating a patient at the end stages of life.

Every session, far-right social conservative groups like Texas Right to Life attempt to weaken the Texas Advanced Directives Act, and every session the medical community is challenged with stopping those efforts. This session, advocates from both TNS and TMA worked hard to ensure that this bill met its demise in the House Calendars Committee, without subjecting members to a difficult vote on the House floor that could be used against our legislative allies in future elections.

SURPRISE BILLING

Dealing with a common complaint of patients, a negotiated agreement between medicine, hospitals, and the health plans creates a new practice that will remove the patient from the mediation process and effectively end the practice of balance billing. The new arbitration process will focus on benchmarks of a floor of average rates and a ceiling of the 80th percentile of billed charges. This is market-based data that will likely be utilized through the FAIR database, a not-for-profit, independent third-party data broker.

Patients may choose to utilize out-of-network services which would result in potentially receiving a balance bill only if they sign an acknowledgement accepting responsibility for these potential costs.

This was the most contentious debate that medicine had that made the finish line of this Legislature. How it manifests in the real marketplace is the big question with enactment coming January 1, 2020.

PRIOR AUTHORIZATION

The Legislature sent SB 1742 to the Governor this week as a transparency measure for pre-authorization practices, which presented a common theme of the 86th. The bill requires insurers to include more detailed contact and specialty information in their physician and facility directories, and make pre-authorization policies accessible online to patients. Patients must be notified of any amendment or removal to existing pre-authorization policies at least 60 days before the change goes into effect. Insurers who fail to publish these changes must provide patients with an expedited appeal for the service or treatment in question. Prior to issuing an adverse determination, SB 1742 requires utilization review agents to facilitate a dialogue between the insurer and a physician regarding the adverse determination in the context of the patient's treatment plan. Ultimately, the bill also calls for the creation of an 8-member appointed Joint Interim Committee to study and propose pre-authorization and utilization review reforms.

HB 3041, which also passed out of both chambers this month, streamlines the pre-authorization renewal process by allowing renewal request paperwork to be submitted at least 60 days prior to pre-authorization expiration. This prevents unnecessary and avoidable gaps in patient care.

Both of these bills amount to positive change, but there's still room for improvement on this patient-facing issue. TNS and TMA will remain engaged throughout the interim during the work of the Joint Interim Committee on prior authorization in hopes of making even greater improvements in 2021.

TNS 2019 Summer Conference JULY 26-27

HOUSTON MARRIOTT MARQUIS

Please join us on July 26 and 27 at the Houston Marriot Marquis for the 2019 TNS Summer Conference.

Nationally recognized speakers will cover diverse topics including updates on new treatments for headaches and depression, ethics CME addressing advanced care planning, business topic dealing with maximizing revenue in private practice, video case studies in refractory CIDP, the microbiome and the gut brain axis, smell and taste disorders in clinical neurology and REM sleep behavior disorder.

Do not miss this opportunity to get CME credits, socialize with colleagues, and relax in this family friendly resort-like hotel in downtown Houston.

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Congratulations to the 2019 Winter Conference Poster Winners!

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The AAN Advocates Educate Congress On Key Issues During Neurology On The Hill

Michael Markowski, DO, FAAN, Vice-Chair, AAN Advocacy Committee

I was thrilled to be back in Washington, DC, with 214 neurologists from 48 states advocating for our patients and colleagues. It has been incredible to see the growth of Neurology on the Hill (NOH) over the past 16 years as this event creates the foundation for so many crucial relationships with members of Congress. Advocacy efforts such as NOH have permitted critical access to legislators, the Centers for Medicare & Medicaid Services (CMS), and other government representatives who have the ability to change our medicine practice significantly, for better or worse.

Prior to NOH, the AAN and my colleagues on the Government Relations Committee choose three issues to address based on AAN member surveys, while factoring any current legislation which we could support. This year, our NOH "asks" were preserving access to neurologists, addressing the rising costs of medications and step therapy exceptions, along with increased funding for vital neurology research. With many recently elected first-term representatives, it was essential to again explain the vital role of neurologists and the myriad of chronic, complex, and often incurable diseases we treat. One out of six people has a neurological disease, costing our health care system over $600 billion per year.

First, we discussed the need to preserve access to neurologists and value the cognitive care we provide, specifically by opposing the CMS proposal to consolidate the current evaluation and management (E/M) codes. The median neurologist receives 75 percent of their reimbursement through these E/M codes, which have been unchanged since 1997. We were collectively shocked in July 2018 when CMS proposed to consolidate the five E/M codes down to two, significantly reducing payments for complex patients, disproportionately affecting patients with neurological diseases. Due to a swift response from the AAN along with many physician and patient groups, this proposal was ultimately delayed for two years. The AAN advocacy efforts helped lead to a bipartisan letter signed by 90 members of the House of Representatives and 24 senators opposing the cuts. This proposal was "budget neutral" per CMS, however, it would have been very harmful to our patients. During NOH, we encouraged our legislators to oppose any payment policy which would further devalue complex E/M services and preserve patient access to neurologists.

The second issue we discussed was the outrageous cost of prescription medications and one of its downstream effects, insurance mandated "step therapy." One in four Americans has problems affording prescription medications, yet little been done to decrease costs. Medications to treat neurological diseases are among the most expensive on the market, including several older generic medications which have increased significantly over the past decade, some greater than 1,000 percent since 2005. The timing of NOH was fortuitous, coinciding with the Senate Finance Committee hearing with CEOs of seven major pharmaceutical companies about drug pricing.

Due to the absurd cost of medications, insurers are intruding upon our doctor-patient relationship through mandates such as "step therapy." Also known as "fail first" therapy, insurers commonly mandate certain medications prior to authorizing the prescribed medication, which has caused much frustration in my community neurology practice on Cape Cod. At NOH, we encouraged our representatives to cosponsor the bipartisan Restoring the Patient's Voice Act of 2019, which requires group insurance to make exceptions to step therapy in certain circumstances including if the medication is contraindicated, unsafe, or the patient is currently stable on an effective treatment.

Similar to recent years, our final request was increased funding for neurological research. We again requested an increase in NIH funding along with robust support for the BRAIN Initiative. In addition, we requested re-authorization of the Patient-Centered Outcomes Research Institute (PCORI), a unique federal program which funds head-to-head medication trials not supported through the NIH or industry. Neurology is one of the top three specialties funded by PCORI, which is set to expire on September 30, 2019.

It was wonderful to work with so many dedicated colleagues across the country as their efforts at NOH will pay dividends for our patients.NOH has allowed me to foster a relationship with my senators and my congressman, Rep. Keating, who I have met with personally for the past several years and has become a strong supporter of neurologists and our patients. In addition to our advocacy efforts, NOH participants were fortunate to learn from Surgeon General Vice Admiral Jerome M. Adams, MD, MPH, along with hearing Susan Schneider Williams, the widow of Robin Williams, share her amazing story of their battle with Lewy Body dementia. Sharing our patient stories is our most effective method to convince legislators to act upon our behalf.

Migraine Auras: A Rare Case of Alice in Wonderland Syndrome

Daniel McNavish
Medical Student Class of 2020
UTHealth McGovern Medical School

INTRODUCTION

Around 35 million people suffer from migraines in the United States per year. A migraine is a headache that can include any part of the head or face. Diagnostic criteria include at least 5 attacks that include these three criteria.[1] An attack lasting 4-72 hours (untreated or successfully treated).[2] The headache including at least two of the following characteristics: unilateral, pulsating, moderate or severe pain intensity, or aggravated by or causing avoidance of routine physical activity.[3] During the headache at least one of the following: Nausea and/or vomiting or photophobia and phonophobia.

An aura is a prodrome before the headache phase that occurs in about 30% of migraineurs. A migraine aura can present as multiple different features. It can present with fortification spectra of jagged lines which moves and leaves transient visual loss behind; it may be colorful or black and white flashes similar to a kaleidoscope in a semicircle shape surrounding an area of transient visual loss. But an aura can also occur with sensory symptoms of unilateral numbness, tingling, or pins and needles in the hand which may spread to the face which occurs in 30% of migraineurs with aura. Transient dysphasia occurs in 20% and can often be mistaken for symptoms of a stroke. When more than one type of aura occurs it usually follows a systematic succession beginning with visual, then sensory, and then dysphasia.

And in some patients a stranger aura can present itself, one which can blur the lines between a fantasy novel and the real world.

CASE REPORT

A 27 year old woman presents to the clinic with the complaint of a headache a month prior that was different from her normal headaches. An avid exerciser, the patient reports that after running a 10k in which she did not feel she overexerted herself, while enjoying her after-run brunch, she started to notice that her arms seemed different than they usually do. She told her family that her arms looked longer than they actually were. She had full range of motion, full dexterity of her fingers, but to her she felt like her hands and arms were further away than she knew they were. This feeling lasted for around 1 hour and was followed by numbness and tingling of her right hand up to her elbow, a large part of her vision becoming distorted and then going dark which lasted for around 1 hour, and trouble speaking with no trouble understanding. She then felt the headache come on which is usual in type and intensity to the ones she is used to.

She has a history of bitemporal pressure-like, non-throbbing headaches since childhood that occur once every other month with an intensity of 6-7/10. These headaches last for about 6-8 hours and involve photophobia and phonophobia but with no nausea or vomiting. She reports that she never has any vision changes during these headaches, trouble speaking, or numbness or tingling in her extremities. Her headaches are usually relieved by acetaminophen in 6-7 hours. She reports knowing the triggers that bring on these headaches: lack of sleep, dehydration, stress, and over exercising without eating.

The patient has a history of Ulcerative Colitis in remission for 3 years and an intracranial cyst diagnosed at age 2 treated with a cysto-peritoneal shunt which was left in place. She takes Mesalamine and OCP's. At the time she was on Estrogen-Progesterone combined but is currently on Norethindrone progesterone only pills due the higher association of stroke in patients that have migraine with aura who take combined oral contraceptives. She has a family history significant for a father with migraines with auras.

Her family took her to the ED where she was given an NIH stroke scale of 4. CT Head showed no acute intracranial abnormality with a shunt in the left temporal lobe. CTA Head/Neck showed no intracranial bleed, occlusion, aneurysm, or stenosis but was found to have an incidental Chiari 1 malformation with the left tonsil protruding 7.4 mm below the foramen magnum. The stroke was ruled out. By the morning her symptoms had resolved and her headache was gone with the neurology team reporting the event as a complicated migraine.

DISCUSSION

Alice in Wonderland Syndrome (AIWS) is an episode of visual or perceptual distortions of surrounding objects or body parts that can last from 10 minutes to up to a month. It is named after Lewis Carroll's fictional character Alice who drinks a bottle labelled "DRINK ME" which causes her to become "now only 10 inches high…" and later she eats a piece of cake which is labelled "EAT ME" which "when she looked down at her feet, they seemed to be almost out of sight. They were getting so far off." This illusion of limbs seeming further away than they actually are is the symptom our patient experienced when looking at her hands when eating her brunch.

The symptom this patient experienced is called teleopsia, when objects appear further away than they actually are. Other manifestations of AIWS include micropsia where objects appear too small, macropsia where objects appear too large, and pelopsia where objects appear closer than they are. Some reports include a sense of time speeding up or slowing down. The condition is in terms of perception only, the eye itself is not affected only the brains processing of the images is altered.

These neurological illusions need to be differentiated from

psychiatric psychosis or hallucinations. While reports of schizophrenia, psychotic disorders, and psychoactive drug intoxications (mescaline and other hallucinogenics) can lead to visual or perceptual distortions, research into these distortions has been done due to the comorbidity in people with reports of AIWS occurring during complex partial seizures, migraine headaches, in children with Ebstein Barr virus (mononucleosis) infections, cerebral lesions, and as a side effect of medications (topirimate).

Imaging modalities have been used as a looking glass into our craniums to obtain a glimpse into the mechanics of AIWS. MRI case reports have found that visual and auditory hallucinations (both of which are hallmarks of AIWS) can occur in malformations of the vasculature of the right temporo-parietal region. In one study, SPECT was used to observe oxygenation perfusion in patients acutely experiencing AIWS, and abnormal blood flow was found localized to the temporal, occipital, and adjacent perisylvian fissure all of which are involved in the visual pathway and the visual cortices. In another study, F-MRI was used to observe a 12 year old boy experiencing micropsia which showed increased activation in parietal lobe cortical regions with a reduced activation in primary visual and extrastriate cortical regions (the extrastriate body area is used in the perception of human body parts). It seems that through these imaging studies that the symptoms of AIWS can be localized to the temporo-parietal junction and the visual pathways in the occipital lobes.

For our patient who experienced AIWS as a migraine aura, no further workup is needed. The patient had a typical migraine with aura with an atypical aura symptom. Therapy for AIWS as a migraine aura is the same as for other forms of migraines: acute and/or prophylactic medications which are tailored to the patient.

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A Rare Case Of Mucormycosis Clivus Osteomyelitis Presenting With Stroke-Like Symptoms

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INTRODUCTION

Skull base osteomyelitis (SBO) is a rare, life-threatening condition with an estimated 30% mortality rate that is mostly seen in elderly, diabetic, or immunocompromised patients.[1] It typically results from an otogenic source with *Pseudomonas aeruginosa* a frequently reported pathogen.[2] Patients often present with non-specific symptoms such as a headache and cranial neuropathies.[2-4] Osteomyelitis secondary to sinonasal infections rarely involves the skull base and more commonly involves the frontal bones and maxilla.[5] Fungal pathogens are rare causes of skull-based osteomyelitis.[6] Here we present a case of SBO caused by *Rhizopus arrhizus* due to sphenoid sinus disease in a patient who presented with stroke-like symptoms.

CASE REPORT

A 50-year-old Hispanic male with a past medical history of hypertension, type 1 diabetes mellitus A1c 7.8, and Marfan syndrome presented with one week of headache and jaw pain. Initial evaluation was notable for elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) and normal non-contrasted brain magnetic resonance imaging (MRI). He was discharged with a diagnosis of sinusitis and temporomandibular joint (TMJ) arthritis and treated with oral prednisone.

He returned six days later with worsening headache, double vision, right-sided facial droop, slurred speech, and vertigo. On neurological exam, he had anisocoria, direction-changing nystagmus, left eye exophoria, and difficulty with tandem gait. Head computed tomography (CT) showed sphenoid sinus disease without acute intracranial abnormalities.

Laboratory studies were notable for a leukocytosis of 14.5, and an elevated CRP of 10.9 mg/dL increased from 3.7 mg/dL on prior admission. Contrasted MRI/MRA of the brain and neck showed enhancement of the clivus, adjacent sphenoid sinus thickening, and dural enhancement tracking to right internal auditory canal, with prominent circumferential enhancement of the mid portion of the basilar artery wall (Image 1). These findings were suggestive of clivus osteomyelitis secondary to sphenoid sinus disease with intracranial spread. The diagnostic angiogram showed infectious vasculitis of bilateral vertebral and basilar arteries with budding basilar pseudoaneurysm (Image 2).

The patient underwent sphenoidotomy and had intraoperative findings of purulent debris, fungal elements in the sphenoid sinus, and necrotic bone. He was empirically started on vancomycin, meropenem, posaconazole, and liposomal amphotericin B. His hospital course was complicated by progression of the infection with prepontine fungal abscess formation and cavernous sinus thrombus (Image 3). Endoscopic clivectomy was considered however patient was deemed not a surgical candidate.

The initial tissue histology from sphenoidotomy showed a large focus of fungal hyphae on H&E with dense mixed inflammation and areas of fibrinoid necrosis. Bacterial cultures demonstrated no growth and however aseptate hyphae grew on fungal culture after one week. Patient was transitioned to liposomal amphotericin B, posaconazole and Micafungin was added for potential synergy. His treatment course was complicated by acute kidney injury secondary to liposomal amphotericin B requiring a dose reduction. *Rhizopus arrhizus* was confirmed using phenotypic and DNA sequencing through the Fungal Testing Laboratory at the University of Texas Health Science Center. He underwent 18 hours of hyperbaric oxygenation therapy over 12 days. Serial imaging demonstrated radiographic stability, and after approximately 12 weeks of parenteral antifungal therapy, the patient was transitioned to oral posaconazole monotherapy and discharged.

Patient did not have recurrent neurologic symptoms and his repeat imaging showed decreased size of basilar pseudoaneurysm one year after discharge. He was recommended to continue oral posaconazole until resolution of imaging abnormalities.

DISCUSSION

SBO is described in the literature as a rare, life-threatening sequela of ear or sinonasal infections, particularly in elderly diabetics and the immunocompromised.[2,7] The infection most commonly occurs secondary to otitis externa, spreading contiguously from the ear canal to the skull base, primarily affecting the temporal bone.[8] Clival osteomyelitis not associated with an otogenic source is an atypical manifestation of this disease.[3] Poor bone vascularization seen in conditions such as coronary artery disease and diabetes increases susceptibility to SBO.[1] Other risk factors include human-immunodeficiency virus infection and long-term steroid use.[9]

Symptoms of clivus osteomyelitis are often non-specific. The clinical presentation varies widely and is dependent on the severity and anatomical progression of infection at initial presentation.[3] The most consistent complaint is persistent headache or facial pain, followed by various cranial nerve (CN) palsies.[1,8-11] Other reported symptoms include proptosis, amaurosis, facial edema, dysphagia, hoarseness, reduced hearing,

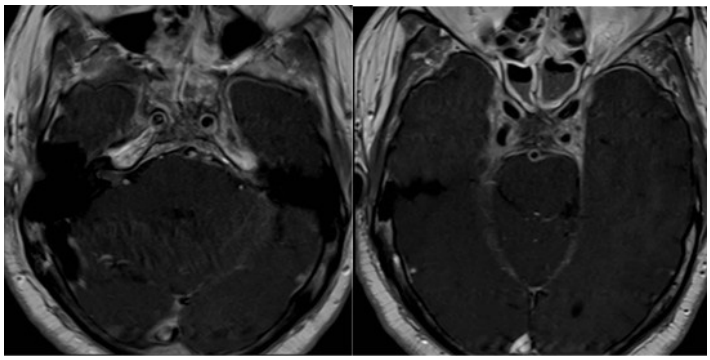

Image 1: Contrasted MRI T1 sequence showing clivus and dural enhancement tracking to the right internal auditory canal as well as circumferential enhancement of the basilar artery

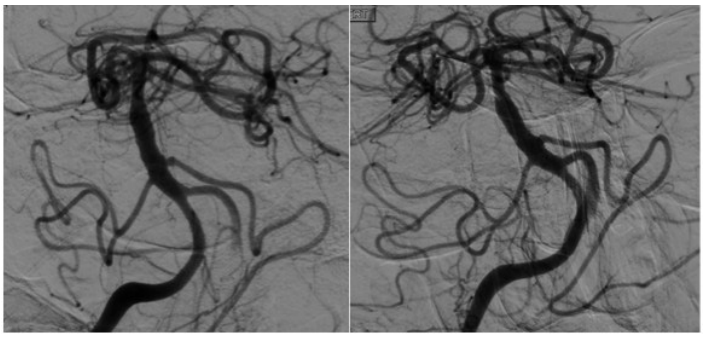

Image 2: diagnostic cerebral angiogram showing vertebral artery vasculitis and basilar pseudoaneursym

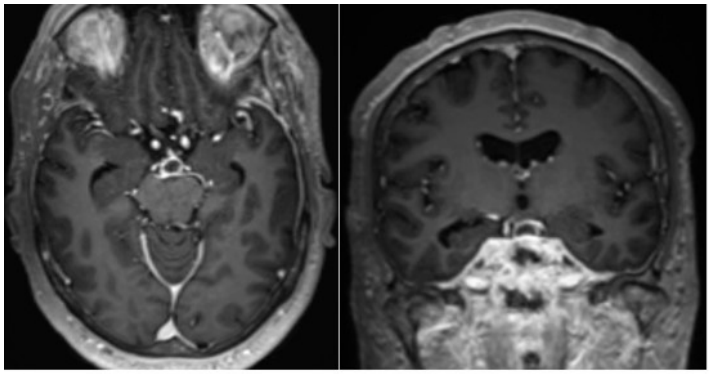

Image 3: contrasted MRI T1 sequence showing fungal epidural abscess extending into prepontine cistern with surrounding leptomeningeal enhancement

diplopia, nausea, vomiting, and weight loss.[3,12,13] Deficits in CN VI, IX, X, XI suggest clival involvement because of its anatomical location.[3,14,15] Although sometimes associated with chronic or ineffectively treated sinonasal infections, in a study of 42 cases of clival osteomyelitis, only 24% of patients presented with nasal discharge or congestion.[16] A unique finding in our patient was nystagmus likely due to vestibular nerve involvement secondary to the infection spreading to the internal auditory canal, which was evident on subsequent contrasted MRI. The rarity of this condition in addition to the nonspecific symptoms at initial presentation can delay diagnosis and treatment. In our patient his initial non-contrasted MRI was unrevealing and he was misdiagnosed with sinusitis and TMJ.

Mucormycosis is well described as rhinocerebral presentations.[13,17] The progression to SBO is rarely described and is mostly a late diagnosis of invasive disease.[18,19] Of note, our patient had an atypical presentation of SBO due to *Rhizopus* infection of the sphenoid with later complications of brain abscesses and infarction. Mucormycosis is a fulminant opportunistic infection mainly afflicting immunocompromised individuals. The incidence is about 500 annually in the U.S.A with 95% of the cases caused by *Rhizopus* spp.[12] Uncontrolled diabetes mellitus is one of the main predisposing factors along with hematologic disorders.[20] *Rhizopus* spp. are inhaled and invade deep tissues particularly in hosts that have favorable conditions where neutrophil function is impaired.[12,21] Studies have shown that the organism proliferates in ketoacidosis states due to its ability to produce ketoreductase, which explains its association with diabetes and diabetic ketoacidosis.[20] The usual route to the CNS is from the nose to ethmoid sinus then to the retro-orbital region. However, it may also progress via the sphenoid sinus as was seen in our patient.[22]

Other than the invasion of the soft tissue, *Rhizopus* spp. can spread through vascular structures leading to pseudoaneurysm and intracranial abscess formation as well as thrombosis and infarcts.[23-25] The angioinvasive nature of *Rhizopus* spp. usually causes bony involvement to be the last stage of the disease after complications from deep soft-tissue infiltration.[11,17] In contrast, our patient initially presented with involvement of the skull base and later developed a pituitary abscess, cavernous thrombosis, and a pontine infarct.

Diagnosing clivus osteomyelitis and identifying the causative pathogen promptly is critical, as early treatment is necessary to reduce mortality and morbidity and to reduce the risk of complications such as cavernous sinus thrombosis, meningeal spread, and death.[3] Sadly, due to the nonspecific presentation and rare nature of this disease, delays in diagnosis and misdiagnoses have been commonly reported in the literature.[10,15,26,27] In the late stages, CT imaging may show evidence of bone erosion, but initially, imaging findings can be normal, as was the case with our patient.[9,28-30] MRI, particularly T1 sequence, can better identify minor skull base abnormalities and is the imaging modality of choice for screening.[11,12,27] Additionally, MRI can identify intracranial complications such as thrombosis, infarcts, and abscesses, which are frequent occurrences in invasive mucormycosis.[11,17,31] In our patient, the diagnosis was made by initial MR imaging and tissue histology. The pathogen was later confirmed with culture results.

Treatment of rhinocerebral mucormycosis due to Rhizopus spp. generally includes systemic amphotericin B, surgical removal of infected tissue, and reversal of any immunocompromising state.[13,20,25] One study demonstrated high survival rates with radical surgical intervention consisting of abscess drainage and bone resection.[1] Although surgical management has not proven to lead to improved mortality, many case reports recommend aggressive surgical debridement and tissue resection in the management of fungal osteomyelitis.[1,32] In one case of invasive mucormycotic anterior skull base osteomyelitis, aggressive removal of the infected bone through an infratemporal fossa approach was critical to the patient's improvement.[32] Unfortunately, our

Continued on page 12

patient was deemed a high surgical risk for further invasive debridement of his clivus bone and as such relied heavily on antifungal therapy as the mainstay of treatment.

Amphotericin B is the most widely reported initial antifungal in the treatment of invasive mucormycosis.[33-36] Our patient developed acute kidney injury while on liposomal amphotericin B but was able to tolerate lower doses of the medication. Mucormycosis is intrinsically resistant to echinocandins but they may play a synergistic role with amphotericin in treatment.[34,37] Posaconazole is a triazole effective against many of the pathogens that cause mucormycosis, including *Rhizopus*.[35,38] An early study looking at posaconazole as salvage therapy for treatment of invasive fungal infections reported high rates of partial response and cure.[39] The newer oral delayed-release tablet has a better-reported bioavailability than previous formulations and was used for our patient.[35] Lab testing revealed susceptibilities for triazoles and amphotericin B. Based on available pharmacokinetic data and serum drug levels it was deemed that posaconazole was a reasonable treatment for this patient.

Additionally, hyperbaric oxygen therapy (HBO) has been shown to provide clinical benefit when used as an adjuvant. One study noted improvement in prognosis using HBO as fungal growth was inhibited by increased oxygen tension.[40] It has been shown that fungal growth was reduced in vitro via decreased tissue death by HBO.[41] One case report noted no evidence of relapse disease at 16 months follow up in an insulin dependent patient after adjuvant treatment with hyperbaric oxygen therapy.[42] The proposed theory of why HBO may be beneficial is that the hypoxic state of infected bone tissue hinders the ability of neutrophils to produce reactive oxygen species necessary for antimicrobial activity. By decreasing hypoxia within soft tissue and bone, the phagocytic ability of neutrophils is improved, and increased oxygen tension enhances osteogenesis as well as angiogenesis.[3] One study showed that the combination of antimicrobials and adjuvant 30-day HBO treatment for three sessions of 30 minutes each day showed complete resolution of infection.[43] However, no large study to date has evaluated the use of HBO with regards to clival osteomyelitis.

CONCLUSION

Invasive SBO although rare, is a progressive and devastating disease if not managed properly. A high index of suspicion is needed especially in patients with risk factors presenting with sinusitis, cranial neuropathies or other neurological symptoms given the angioinvasive nature of Rhizopus spp. Although histological diagnosis of tissue biopsy is required, prompt MRI should be obtained as CT findings can normal, as was the case in our patient. Prompt initiation of antimicrobial therapy and surgical debridement before culture results is critical to successful treatment of the infection. The role of hyperbaric oxygen therapy is not yet well defined but may be beneficial and cost-effective as adjuvant therapy.

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A Rare Case Of Painful Nervus Intermedius Neuropathy Responsive To Sphenopalatine Ganglion Blocks

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Nervus intermedius neuralgia (NIN) is a rare debilitating condition characterized by brief paroxysms of pain, felt deeply in the auditory canal, for which the treatments include antiepileptic medications, invasive nerve blocks and intracranial surgery. Here we report a case of NIN where the patient responded well to repeated courses of transnasal sphenopalatine ganglion (SPG) blocks.

A 34-year-old healthy female was referred to the neurology clinic by her ENT surgeon for complaints of sudden onset of debilitating severe, stabbing deep left inner ear pain that started six months ago. No antecedent triggers including zoster or exposure to tick bite were reported. The pain occurred daily as single jabs lasting 2-3 seconds, repeating continuously while awake, with rare 30--60 minute breaks. Except for occasional radiation to the angle of the mandible on the left side, no other referral pattern or cutaneous triggers were described. Non-narcotic and narcotic analgesics did not help.

Pertinent past surgical history included translabyrinthine resection of left schwannoma eight years ago. Postsurgical complications included crocodile tears (suggesting involvement of nervus intermedius), total left hearing loss and mild left facial paresis.

Physical, neurologic and ENT evaluations were negative except the above-mentioned findings. Extensive lab studies and audiology evaluations were noncontributory. High resolution 3 T MR imaging with and without contrast showed "postsurgical changes with a patulous left internal auditory canal and nodular enhancement at the inferior aspect of the fundus measuring 2x 1 mm", essentially unchanged since her surgery. The proximal segment of NI ,but not the canalicular segment was visualized.

The patient was started on carbamazepine XR 100 mg twice daily with plans of uptitrating the dose. She was unable to tolerate more than 100 mg a day due to disabling side effects and was kept on this subtherapeutic dose. Gabapentin could not be tolerated either. SPG blocks were started using the standard protocol with Tx360 (®) device, bi-weekly for 6 weeks (1).

Patient reported 50% response after the third block and 100% relief after the fourth block. The relief was maintained for 5 months when the pain recurred after cold exposure. A repeat course of SPG blocks resolved this pain. The third recurrence of pain occurred again due to cold exposure 5 and a half months later and she is receiving SPG blocks currently with similar good response.

Nervus intermedius (NI) is the sensory and autonomic branch of the seventh cranial nerve (CN VII) and travels with the CN VII motor division in the facial canal after exiting from the pons. Though first identified by Eustachius (1563), the first clear documentation of the NI was given by H.A. Wrisberg in 1777. In 1908, Ramsay Hunt associated geniculate neuralgia (now termed NIN), with herpes zoster (2).

The NI branches into greater superficial petrosal nerve (GSPN) and chorda tympani at the geniculate ganglion without synapsing there. GSPN travels to and synapses with the SPG, which is the major extra cranial parasympathetic structure, lying in the pterygopalatine fossa. The SPG also receives sensory (V2) and sympathetic fibers and projects the postganglionic parasympathetic fibers to the lacrimal gland, mucosa of the facial bone and extra and intracranial vasculature (3). SPG blocks have been used successfully in various headache syndromes, facial pain and facial neuralgia, probably utilizing this complex pathway.[3] We postulate that SPG blocks can modulate and inhibit the painful impulses traveling via the afferent NI fibers which synapse with the trigeminal nucleus caudalis in the brainstem, probably explaining the remarkable response this patient achieved.

This patient met the diagnostic criteria for NIN as per the international classification of headache disorders-3rd edition, (ICHD-3) except for lack of trigger areas (refer to ICHD-3 for complete diagnostic criteria). We postulate that this is a case of painful postsurgical nervus intermedius neuropathy (PPNIN : 13.3.2), probably due to scar tissue formation, as no other identifiable cause was present.

Literature on NIN is scanty and to our knowledge, this is the first case of PPNIN responsive to repeated SPG blocks. This case is unique in that the neuralgic pain started eight years after surgery and showed excellent response to a non-invasive safe therapy, lasting up to 5 months.

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Thermoregulatory Dysfunction in a Patient with Locked-in Syndrome Due to Bilateral Ventral Pontine Infarction

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BACKGROUND

Locked-in syndrome (LIS) is a well-described, rare neurologic disorder classically characterized by quadriplegia, multiple cranial nerve palsies and mutism with the preservation of vertical eye movements. Incomplete variants exist in which horizontal eye movements are preserved with variable extremity mobility. The most common etiology is either pontine hemorrhage or thrombosis of the basilar artery but can be due to any lesion of the ventral pons and midbrain to include infections, inflammation, mass effect, trauma, late-stage amyotrophic lateral sclerosis or demyelinating lesions[1, 2]. Prognosis is variable with a wide range of potential recovery possible based largely on the underlying etiology. Mortality has been reported as high as 60%, with non-vascular etiologies associated with better outcomes[2].

Central hyperthermia, sometimes referred to as neurogenic fever or fever of central origin, is a challenging diagnosis traditionally thought of as a diagnosis of exclusion. Central hyperthermia is characterized by rapid onset of hyperthermia, defined as temperatures at least 101^{0}F, negative infectious workup, lack of response to antipyretics and is correlated with a poor prognosis[3-5]. It is typically associated with traumatic brain injury, hypothalamic lesions, and has been reported in stroke, but to date has not been reported with locked-in-syndrome.

The mechanism for central hyperthermia is not well understood but thought to be due to disruption of the thermoregulatory pathways in the brainstem. Several studies have identified brainstem lesions (most commonly hemorrhage) as a common mechanism for central hyperthermia[5-6]. In a prospective study looking at patients who developed fever within 24 hours after stroke, brainstem hemorrhage was the most common cause at 64% with the majority of those involving the pons. Basilar infarction was the cause in 3% of the patients studied[5]. There are multiple structures in the brainstem postulated to play some role in thermogenesis. The lateral parabrachial nucleus at the junction of the pons and midbrain has stimulatory projections to the preoptic area in the hypothalamus which then leads to increased core body temperature through various mechanisms such as brown adipose tissue thermogenesis and cutaneous vasoconstriction[4,6]. Sympathetic input travels through the brainstem which also plays a role in stimulating brown adipose tissue thermogenesis[6]. Animal studies have also confirmed that tonic inhibitory heat production signals from the brainstem cause hyperthermia when lesioned[4]. Although less commonly, hypothermia can also result from disruption of these same thermoregulatorypathways.

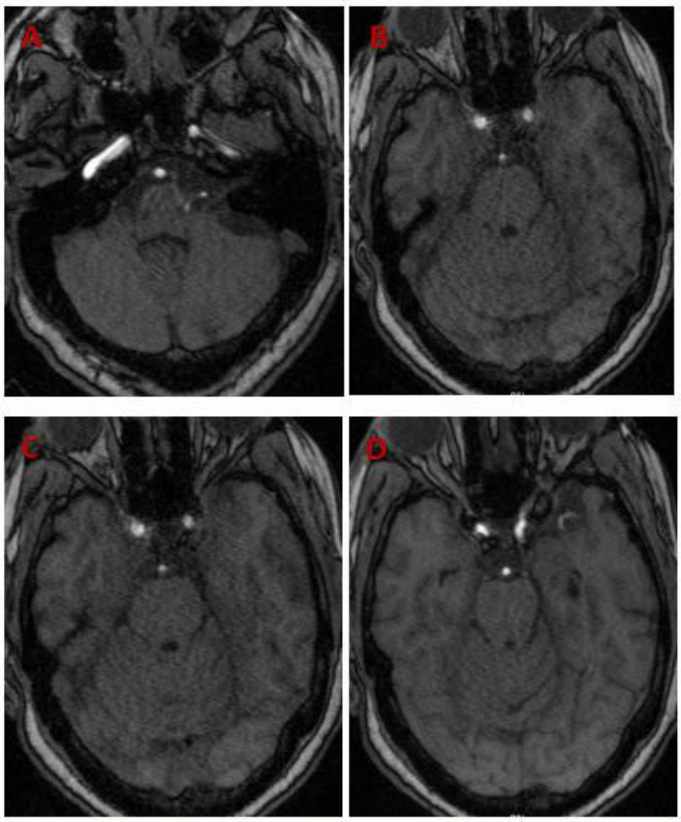

Figure 1: Magnetic Resonance Angiogram

Severe proximal basilar artery narrowing (B and C) without occlusion or thrombus.

Neurologic causes of central hypothermia are similar to that of central hyperthermia and include Parkinson's disease, multiple sclerosis and traumatic brain injury[7-10].

CASE REPORT

A 71-year-old female with a past medical history of hypertension presented to our Emergency Department after being found down and unresponsive with the last known well time approximately 5 hours prior. At the time of initial neurologic exam, the patient was intubated and sedated with etomidate and propofol and paralyzed with rocuronium. Initial systolic blood pressures on arrival were recorded between 130 and 140 but soon increased, requiring a nicardipine drip to maintain a blood pressure less than 220/110. Rectal temperature at that time was 93^{0}F. Initial non-contrast CT head was without acute abnormality and CT angiogram did not show a thrombus. A rapid MR showed subtle diffusion restriction in the pons which was thought to be artefactual by the radiologist and corresponding MR angiogram showed a narrowed but patent basilar artery without thrombus (Figure 1). tPA was not administered as her last known well was outside of the treatment window. While on a propofol drip, electroencephalogram (EEG) showed continuous generalized slowing without epileptiform activity or electrographicseizures.

Once sedation was weaned, neurologic exam revealed an alert but non-verbal patient, with complete quadriplegia and absence

of volitional facial movements except for eye blinking with preserved vertical and horizontal eye movements. The patient was able to answer questions through blinking and endorsed pain in all extremities. She also demonstrated reflexive yawning and intermittent bilateral upper extremity extensor posturing without any EEG correlate. Reflexes were preserved with hyperreflexia in her upper extremities and bilateral upgoing toes in the lower extremities.

7 hours after arrival, the patient developed a fever of 100.8°F. A full infectious workup was completed, to include blood, urine and sputum cultures and lumbar puncture, all of which were unrevealing. Repeat MRI brain obtained on hospital day 2 showed bilateral ventral pontine infarction with midbrain involvement (Figure 2). The patient's 12-day hospitalization was complicated by persistent hyperthermia up to 101.5°F despite treatment with antibiotics, antipyretics and cooling blankets. Blood, urine and sputum cultures were repeated frequently throughout her hospitalization but were all negative. At time of discharge, her temperature had begun to normalize over the prior 12 hours and she had regained the ability to volitionally tap her left index finger.

DISCUSSION

The clinical presentation of locked-in syndrome is due to lesion of the ventral pons disrupting the corticospinal tracts bilaterally. These patients classically have preserved vertical eye movements along with preservation of consciousness and sensory pathways. They retain the ability to blink volitionally due to sparing of the supranuclear motor pathways. Our case demonstrates an incomplete variant with intact vertical and horizontal eye movements. As in this case, involuntary motor phenomenon including yawning, crying, laughing, ocular bobbing and posturing have been reported in the literature[2, 11]. These stereotyped movements are postulated to emanate from subcortical structures. Electroencephalograms (EEG) in locked-in patients show no electrographic correlation with this stereotyped motor activity, as was the case in our patient. EEGs are not needed to confirm the diagnosis of LIS; however, an EEG showing a relatively normal waking background that is reactive to stimuli should raise concern for LIS in a patient thought to be comatose.

In addition to being an incomplete variant of LIS, our case is unique due to the concomitant presence of significant thermoregulatory dysfunction. Central hyperthermia is well described in patients with traumatic brain injury, lesions of the hypothalamus, and acute stroke[3, 5], but to our knowledge has not been described in adults with locked-in-syndrome. Our patient demonstrated fevers that were refractory to traditional physical cooling methods and antipyretics in the setting of persistently negative blood, sputum and urine cultures consistent with central hyperthermia. She also had a rapid onset of fever, which is also supportive of the diagnosis. Interestingly, she presented initially with hypothermia before becoming febrile which has also not been described in the literature as part of LIS but is further evidence of disruption of her thermoregulatory system.

Fever of central origin is associated with high mortality and found to be an independent risk factor for mortality in patients with stroke and neurologic injury[3, 5]. Distinguishing fever of central origin vs infectious fevers is a diagnostic challenge but an important distinction given the mortality associated with central fevers and the differences in treatment. Treatment for central hyperthermia is not well established and often difficult with antipyretics having no effect. Treatment is geared towards physical cooling but there have been case reports showing efficacy of bromocriptine and baclofen as potential pharmacologic options[12, 13].

CONCLUSION

Accurate diagnosis is particularly important in patients with locked-in-syndrome to prevent premature withdrawal of care and informing treatment decisions. Differentiating fever of central origin from fever due to infectious etiologies is critical for both guiding treatment options and informing the prognosis for patients and their families. Underlying infections should be addressed promptly with appropriate antibiotics due to the high mortality associated with infection in this patient population. However, it is paramount to recognize that central hyperthermia is also associated with poor outcomes and high mortality with a vastly different treatment paradigm. Although central hyperthermia is certainly reported with pontine lesions and has been reported in basilar artery occlusion, to our knowledge, this is the first reported case of central hyperthermia in the clinical setting of locked-in syndrome.

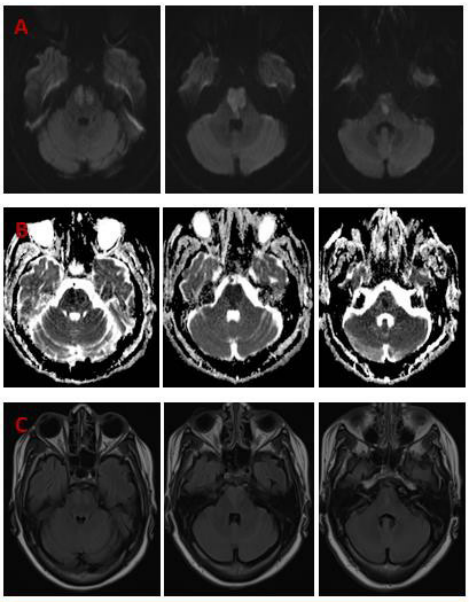

Figure 2: Magnetic Resonance Imaging without contrast

A: Diffusion weighted imaging showing hyperintensity of bilateral ventral pons with extension to the midbrain.
B: Apparent diffusion coefficient showing restricted diffusion in the same distribution.
C: FLAIR sequence showing corresponding hyperintensity.

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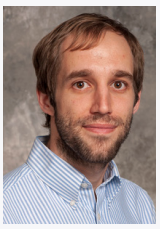
The Spectrum of Anti-Myelin Oligodendrocyte Glycoprotein Associated Disorders



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INTRODUCTION

In recent years, the expanding number of identified autoantibodies targeting proteins throughout the central and peripheral nervous system has driven significant advances in clinical neurology. These novel autoimmune neurological disorders represent an important consideration in patients with acute, progressive neurological symptoms as early recognition and treatment can lead to favorable outcomes. Among demyelinating disorders, the discovery of aquaporin-4(AQP4) antibodies in patients with severe optic neuritis and transverse myelitis defined the neuromyelitis optica spectrum disorders (NMOSD)[1]. This breakthrough led to increased interest in NMOSD, culminating in three novel treatments pending FDA approval[2]. Despite these advances, a significant proportion of patients with atypical demyelinating syndromes remained unexplained.

Myelin oligodendrocyte glycoprotein (MOG) is expressed on oligodendrocytes in the CNS. Antibodies to MOG were initially reported to be detected at high rates in multiple sclerosis (MS) patients, though subsequent studies also detected the antibody frequently in control populations[3]. With improvement in assays for MOG antibodies, it was discovered that anti-MOG antibodies were actually rarely present in MS patients, but were found in a large percentage of patients with various other demyelinating events[4]. Testing for anti-MOG antibodies is now available at commercial labs in the United States and Europe, and it is now apparent that MOG-associated disorders have a broad spectrum of presenting symptoms.

This review covers the manifestations that have been associated with anti-MOG antibodies in the literature, and proposes a general approach to management.

ARE ANTI-MOG ANTIBODIES ASSOCIATED WITH NEUROMYELITIS OPTICA SPECTRUM DISORDERS?

As the clinical presentations associated with anti-MOG antibodies have overlapping features with AQP4 autoimmunity, some argue that the disorder should be classified as a variant of NMOSD[5]. While both disorders harbor a risk of relapse and may require immunomodulatory treatments, there are some phenotypic differences which are highlighted in the sections below. Furthermore, persons with the same clinical presentation have very a different prognosis in MOG related disorders as compared to AQP4. Given these differences, for the purposes of this article we will use the term "MOG-associated disorders" to refer to the spectrum of presentations encountered with anti-MOG antibodies.

ACUTE DISSEMINATED ENCEPHALOMYELITIS

ADEM is a demyelinating syndrome commonly encountered in children that typically presents with an infectious prodrome followed by altered sensorium and focal neurological deficits with white matter lesions of the brain and spinal cord. Anti-MOG antibodies are detected in a large proportion of children with ADEM[4]. MRI demonstrates bilateral, hazy T2 hyperintensities within the white matter, and frequently involves the deep gray matter structures, brainstem, and cerebellum. Simultaneous spinal cord and optic nerve involvement is also a common imaging feature of anti-MOG Ab-positive ADEM[6].

While ADEM was classically considered a monophasic event, it is recognized that some patients develop subsequent demyelinating episodes. Persistent detection of MOG antibodies 6-12 months following an episode of ADEM is now recognized as an important risk factor for future demyelinating events. In one study, the relapse rate among patients with ADEM and persistent anti-MOG Ab-positivity was 88%, compared to 12% among

those with transient positivity. Subsequent relapses typically occurred several years after initial presentation[7].

TRANSVERSE MYELITIS

Anti-MOG antibodies have been detected in patients with transverse myelitis, either in isolation or concurrently with other MOG-associated phenotypes. Similar to AQP4 antibodies, MOG is frequently associated with a longitudinally extensive transverse myelitis that may extend into the posterior medulla. However, several imaging features may provide clues in distinguishing between MOG and AQP4 related transverse myelitis. MOG-positive patients commonly have multiple, noncontiguous spinal cord lesions, and lesions often have minimal contrast enhancement. The conus medullaris is frequently involved in MOG myelitis, and one recent report describes a lumbosacral myeloradiculitis in a MOG-positive patient[8,9].

Recent findings may serve to expand the spectrum of MOG-associated myelopathies. A sup-group of patients with MOG-associated transverse myelitis demonstrate imaging abnormalities that are restricted to the gray matter of the spinal cord, and have flaccid areflexia on evaluation. This may present a diagnostic dilemma for the clinician, as similar findings have been encountered in recent outbreaks of acute flaccid myelitis in association with enterovirus D68[8,10]. Furthermore, recent anecdotal reports suggest anti-MOG antibodies may be found in patients with 'imaging negative' myelopathies[11].

During an acute attack, patients with MOG-associated myelitis frequently have difficulties with ambulation and urinary difficulties, and one-third of patients are wheelchair dependent. However, their long-term outcomes are much favorable compared to other causes of LETM, with only 6% of patients requiring an assisted device for gait[8].

OPTIC NEURITIS

In adults, optic neuritis is one of the most common presentations of MOG-associated disorder. Monophasic optic neuritis, relapsing optic neuritis, as well as chronic relapsing inflammatory optic neuropathy have all been associated with the antibody, as well as syndromes including mixed phenotypes, such as optic neuritis in combination with transverse myelitis, etc[12]. ADEM with optic neuritis has a high probability of being associated with the anti-MOG in children, but is a rare manifestation in adults.

There are three important clues in the diagnosis of MOG-associated optic neuritis. First, acute optic neuritis associated with anti-MOG is more likely to have elevated optic disc margins in comparison to optic neuritis not associated with the antibody. This is consistent with the purported pathogenesis of the antibody as it is associated with an oligodendrocytopathy rather than, say, an astrocytopathy with AQP4-NMOSD. Second is the presence of preserved visual acuity despite severe retinal nerve fiber layer (RNFL) thinning as detected by optical coherence tomography (OCT)[13]. The phenomenon is present in the convalescent stage of the attacks rather than the acute setting, where the visual symptoms seem to be more consistent with NMOSD. Last, and the least studied, is the presence of a retinopathy in combination with the optic neuritis. Peripapillary hemorrhages, retinal hemorrhages and macular starring have been described, which is counter-intuitive with the suspected pathogenesis of the antibody, and leads to phenotypical overlap with infectious forms of optic neuritis As such, careful evaluation including fundoscopy is indicated in acute optic neuritis before embarking on empiric treatment.

CORTICAL MENINGOENCEPHALITIS WITH SEIZURES

More recently a syndrome manifesting primarily as meningoencephalitis with seizures has been described. This phenotype is quite heterogeneous, with a variety of imaging and laboratory associations, including normal imaging though rarely normal spinal fluid studies[14]. There have been reported cases of individuals with concurrent presence of anti-MOG and anti-NMDA antibodies present, but the contribution of each antibody in the development of this syndrome is unclear. Whether these antibodies are directly related to the pathogenesis of this syndrome or an immunological epiphenomenon has yet to be determined. An empiric trial of immunotherapy should be considered once infectious processes have been evaluated, as patients can respond favorably[15]. More study is needed into this association, and in proposing treatment paradigm.

EVALUATION AND MANAGEMENT

Currently, the clinical approach to MOG-associated disorders is similar to the evaluation of NMOSD or multiple sclerosis. A careful history of previous events is crucial, as there may be a remote history of unexplained events for which a patient experienced good recovery (e.g. previous history of unexplained encephalopathy in childhood in an adult with new onset optic neuritis) to suggest a MOG-associated disorder. Certain MRI features, as highlighted in the above sections, may provide further clues to the diagnosis. Even when the history of an attack is absent, there can be structural stigmata of demyelinating events, such as RNFL thinning detected my optical coherence tomography despite normal visual acuity on examination, which has been described in the disease. Similar to other demyelinating diseases, spinal fluid analysis is important to rule out infectious and malignant considerations. Testing for anti-MOG antibodies is available through several commercial labs in the United States, and a recent study showed comparable the rates of detection among several MOG assays available. In contrast to AQP4, CSF testing for anti-MOG antibodies is not currently available in the US[16].

In terms of management, there has been much discussion and opinion with limited long-term outcomes data. In general, for a patient with MOG-associated disorders that experience one demyelinating event, conservative management has been advocated. This strategy arises from the available data suggested overall low risk of relapse, sometimes with a decade between attacks. As current research suggests persistent detection of MOG

Continued on page 18

antibodies is a risk factor for relapses, checking antibodies at regular intervals after the initial event may help inform treatment decisions[7]. Anecdotally the titer of anti-MOG antibody has been associated with risk of relapse. The data on such a strategy are lacking, and with the increasingly diverse phenotype, such a strategy will need continued longitudinal assessment. Once a second clinical attack has occurred, then it is generally advocated to initiate immunomodulatory treatment. The selection of a particular agent is generally urged to fall under the data available for each phenotype. There has been success with both corticosteroids, B-cell depleting therapies, mycophenolate mofetil, and IVIG[17,18]. At this time, the data for assessment and treatment continues to be on the experiential and anecdotal level, and thus evaluation at a tertiary care center should be considered.

CONCLUSIONS

Anti-MOG antibody-associated disorders represent a growing spectrum of demyelinating CNS disease that typically are associated with severe manifestations at nadir, but generally experience good long-term outcomes. Anti-MOG antibodies represent an important diagnostic and prognostic biomarker in patients with acquired demyelination, though its role in predicting relapses needs to be further elucidated. It is generally recommended that patients with more than one attack be engaged in discussions for immunomodulatory treatment.

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