TEXAS NEUROLOGICAL SOCIETY WINTER 2020

Broca's Area

The Voice of Texas Neurology

President's Message
Everything's Bigger in Texas

Edward Fox, MD, PhD

Being a Texas native, I have heard the quote "Everything's bigger in Texas" my whole life. The expression has its origin as early as 1913, but became a popular saying in the 1950s. It's overused and leads to a lot of eye rolls outside of the Lone Star State, but as it turns out, the TNS is a pretty good example of why the saying has stuck around.

According to the AAN website, 24 states have neurological societies. Of those, 16 have a meeting scheduled, not all for continuing education. And none of them have anywhere close to the membership of the TNS. The states bordering Texas have no formal organization for neurologists. Travel up Interstate 35 and you won't see another state society until you hit Des Moines, Iowa. I-10 has a gap between Arizona and Alabama only filled here in Texas.

An email from our esteemed past president Randy Evans stated that he gave a talk to the California group recently. The numbers are remarkable – about 1,500 neurologists in the state, 200 members, and only 60 attendees at the annual educational program over 3 days. So, why the discrepancy between the states? What makes the TNS so different?

I think there are a number of factors at play here, and each played a significant role in the juggernaut that is our organization. The first is that we started early and went state-wide quickly. The first president in 1975 was Sheff D. Olinger, Jr., MD, who was also the first director of Neurology at Baylor Hospital in Dallas. In subsequent years, the presidency marched around the state, attracting interest in multiple locales. The founders were tireless in wanting to grow the organization, and set it up to succeed.

Secondly, the purpose of the TNS included high-level educational programs, not just advocacy. We can all get behind the idea of a high-quality CME experience, and making it the linchpin of the meeting was a fully successful direction. The winter meeting became more popular when it took root in Austin, likely because it was being touted as an opportunity for socialization and was much more predictable for travel plans. The launching of the summer meeting as a family retreat with a briefer, more focused educational program has also been successful.

Advocacy has been very successful here. The state legislature has had a number of physician representatives, and the TMA and subspecialty organizations have been very strong. Money is spent for lobbying and for reporting to the membership, a huge advantage to the practice of medicine. The TNS has joined forces with others as needed, but even as a single voice has successfully both promoted good legislation and squashed bad bills every session.

The sense that neurologists in Texas could work together really took off when the academic institutions added their clout. Department chairs moderating sessions at the winter meeting and the appearance of nationally renounced speakers was a powerful force, and this has been maintained despite the increased number of medical schools in Texas with an enormous geographic sprawl.

Lastly, I do think it is all about the attitude. I consider it special that I have good friends throughout the state that I can look forward to seeing a couple of times a year. It doesn't matter what city you live in, if you are part of the TNS, you can share ideas, jokes, and family stories with a lot of people over a few days. I really don't know why other states can't get their act together and play nice. However, I do know why we can. The state motto of Texas is "Friendship." The word, Texas, or Tejas, was the Spanish pronunciation of a Caddo Indian word meaning "friends" or "allies." It's not just a state advertisement, it's a reality in clear sight. See you soon at the Winter Conference!

CONTENTS

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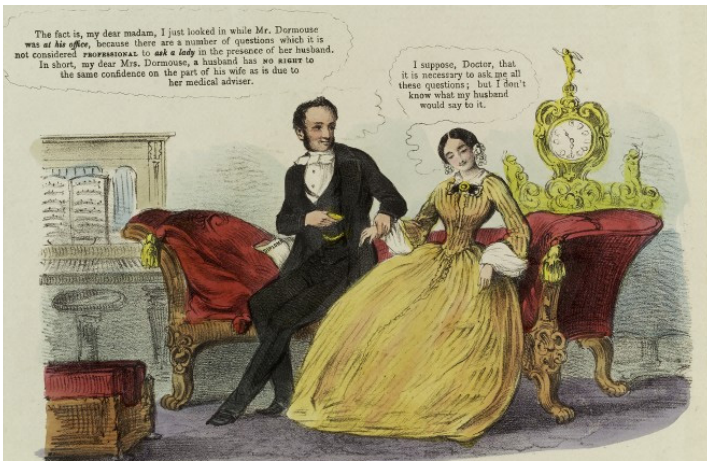
Editor's Notes

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 20th Annual TNS Winter Conference at the Hyatt Regency in Austin. Chaouki Khoury, program director, and the education committee have planned an excellent program.



PHYSICIAN'S WHITE COATS

How do you dress? I wore ties to work for many years until a couple of years ago when I noticed ties were out in hospitals and offices and there were even concerns over ties as a vector for nosocomial infection. I have many lab coats but don't wear them in the office. They seem hot and uncomfortable. Convention seems to be changing. Casual is much more common.

How do you all dress in the clinic? Ties, scrubs, dresses, white coats, jeans? Do patients care?

White coats and bacterial transmission to patients.--White coats are still widely worn in the hospital. Some patients associate white coats with higher levels of confidence and quality of care (Petrilli CM, et al. Understanding patient preference for physician attire: a cross-sectional observational study of 10 academic medical centres in the USA. BMJ Open. 2018;8(5):e021239). However, there have been growing concerns over white coats as a source of pathogenic bacterial transmission (Goyal S, et al. Bacterial contamination of medical providers' white coats and surgical scrubs: A systematic review. Am J Infect Control. 2019;47(8):994-1001).

Bacteria can survive on white coats for up to 98 days depending upon the fabric (shortest survival times with polyester alone compared to cotton and blend fabrics). Surveys have found that up to 65% of health care providers launder their white coats one time or less every 2 weeks. Home laundering may not be done adequately at home as the greatest degree of eradication of gram-positive and negative bacteria occurs when washing with bleach at high temperatures followed by tumble drying and ironing which is often not done.

Since 2007, the UK Department of Health has implemented a policy of bare below the elbows requiring health care providers to wear short or rolled up sleeves and no white coats, jewelry, ties, watches or rings when seeing patients at the bedside with a decrease in hospital acquired infections from 8.2% to 6.4%. Despite this, data showing a direct link between white coats and bacterial transmission are limited.

Why white coats? Physicians dressed in black until the late 19th century as black is still considered to be a formal color (https://journalofethics.ama-assn.org/article/doctors-white-coat-historical-perspective/2007-04; White Coat Ceremony. McMaster University. available athttps://hslmcmaster.libguides.com/hhm/whitecoat). Physicians would dress as a professional gentleman with black frock coat, black pants, white shirt, and a vest of black or a muted pattern crossed by a gold watch chain, and a black hat, tricorn, or top hat. They would wear this formal outfit even in the operating room.

Lab coats were first worn by scientists in the late 1880s for protection. By 1915, physicians were commonly wearing white lab coats to distinguish themselves from older physicians without academic credentials and to symbolize the new era of scientific medicine. In 1993, the late pediatric neurologist, Arnold Gold, at Columbia, instituted the medical student White Coat Ceremony which now occurs at 99% of medical schools.

VICTORIAN-ERA PHYSICIANS AND THE USE OF VIBRATORS TO STIMULATE ORGASM TO TREAT FEMALE HYSTERIA

Charcot, Freud, and hysteria.--Jean-Martin Charcot (1825-1893) created a special ward for non-insane female with "hystero-epilepsy" at the Salpêtrière in Paris and described minor and major hysteria. However, he opined that hysteria was present in females and males. Brouillet's famous painting of Charcot features "Blanche" (Marie Wittman), a celebrity hysteric considered the queen of hysterics who had endured an abusive childhood and was working doing menial jobs in the hospital wards.

Viennese neurologist, Sigmund Freud became interested in hysteria after studying with Charcot during the winter of 1885-1886 which was the origin of his psychoanalytical theory (Bogousslavsky J, Dieguez S. Sigmund Freud and hysteria: the etiology of psychoanalysis? Front Neurol Neurosci. 2014;35:109-25). We continue to struggle with the diagnosis and treatment of psychogenic neurologic disorders (Thenganatt MA, Jankovic J. Psychogenic (Functional) Movement Disorders. Continuum (Minneap Minn). 2019 Aug;25(4):1121-1140; Tolchin B, Martino S, Hirsch LJ. Treatment of Patients With Psychogenic Nonepileptic Attacks. JAMA. 2019 May 28;321(20):1967-1968; Walzl D, Carson AJ, Stone J. The misdiagnosis of functional disorders as other neurological conditions. J Neurol. 2019 Aug;266(8):2018-2026).

The Gross Clinic by Eakins (Philadelphia, 1875)

Victorian-era physicians and the use of vibrators to stimulate orgasm to treat female hysteria—In her 1999 book, "The Technology of Orgasm. Hysteria, the Vibrator, and Women's Sexual Satisfaction ," Rachel Maines discusses the use of new technology to treat hysteria at the end of the nineteenth century:

"When the vibrator emerged as an electromechanical medical instrument at the end of the nineteenth century, it evolved from previous massage technologies in response to demand from physicians for more rapid and efficient physical therapies, particularly for hysteria. Massage to orgasm of female patients was a staple of medical practice among some (but certainly not all) Western physicians from the time of Hippocrates until the 1920s, and mechanizing this task significantly increased the number of patients a doctor could treat in a working day. Doctors were a male elite with control of their working lives and instrumentation, and efficiency gains in the medical production of orgasm for payment could increase income. Physicians had both the means and the motivation to mechanize."

Her book won the American Historical Associations's Feis Award.

Maine's book led to a 2007 documentary (" Passion & Power: The Technology of Orgasm), a 2011 romantic comedy movie ("Hysteria" with Hugh Dancy and Maggie Gyllenhaal), a 2009 Broadway play ("In the Next Room (or The Vibrator Play)") nominated for 3 Tony's, and a Samantha Bee skit

A Clinical Lession at the Salpêtrière by Brouillet, 1887. Participants include Pierre Marie, Joseph Babinski, Henri Parninaud, and Georges Gilles de la Tourette.

FAILURE OF ACADEMIC QUALITY CONTROL

"Maines fails to cite a single source that openly describes use of the vibrator to massage the clitoral area. None of her English-language sources even mentions production of 'paroxysms' by massage or anything else that could remotely suggest an orgasm. … the 19-year success of Technology of Orgasm points to a fundamental failure of academic quality control. This failure occurred at every stage, starting with the assessment of the work at the Johns Hopkins University Press. But most glaring is the fact that not a single scholarly publication has pointed out the empirical flaws in the book's core claims in the 19 years since its release. (Lieberman H, Schatzberg E. A failure of academic quality control: the technology of orgasm. Journal of Positive Sexuality. 2018;4: 24-47)"

"In an interview, Maines said that she has heard variations of the paper's criticism before—and that her argument in The Technology of Orgasm was really only a "hypothesis," anyway. "I never claimed to have evidence that this was really the case," she said. "What I said was that this was an interesting hypothesis, and as [Lieberman] points out—correctly, I think—people fell all over it. It was ripe to be turned into mythology somehow. I didn't intend it that way, but boy, people sure took it, ran with it."

Maines added that she was a little surprised it took so long for other scholars to question her argument, given how admittedly "slender" the evidence she gave in The Technology of Orgasm was. "I thought people were going to attack it right away. But it's taken 20 years for people to even—people didn't want to question it. They liked it so much they didn't want to attack it." (Meyer R, Fetters A. Victorian-Era Orgasms and the Crisis of Peer Review. A favorite anecdote about the origins of the vibrator is probably a myth. The Atlantic. September 6, 2018).

TNS Advocacy Report: Interim Charges in the Texas Legislature

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

During the 18-month period between legislative sessions, the Texas House Speaker and Lt. Governor typically assign their respective chambers a list of issues that they feel merit further investigation before lawmakers return to Austin the following January. These so-called "interim charges" could rightly be understood as a statement of priorities the Speaker and Lt. Governor would each like to see addressed next session… they provide legislators with the opportunity to investigate complex issues more fully, receive expert testimony and policy recommendations, and develop potential legislation.

While the first round of interim committee hearings has yet to take place, the Texas Neurological Society's legislative affairs team has identified a select number of interim charges which we intend to monitor closely in the months ahead:

BALANCE BILLING

House Insurance – Chair: Rep. Eddie Lucio III (D-Brownsville)

Senate Business & Commerce – Chair: Sen. Kelly Hancock (R-North Richland Hills)

Monitor implementation of SB 1264, which prohibits balance billing (surprise billing) and creates a system of arbitration to settle balance bills. The committees will review the Texas Department of Insurance's (TDI) rules implementing the legislation's exception for non-emergency "elective" services to determine whether the rules limit the exception to out-of-network services that a patient has actively elected to receive after signing a written disclosure.

ADULT STEM CELL TREATMENT

House Public Health – Chair: Rep. Senfronia Thompson (D-Houston)

Monitor the creation of the investigational stem cell registry and review HB 3148, which establishes provisions related to the administration and oversight of investigational adult stem cell treatments.

LOW-THC MEDICAL CANNABIS

House Public Health – Chair: Rep. Senfronia Thompson (D-Houston)

Review agency rulemaking for HB 3703, which expands the list of eligible conditions for low-THC cannabis prescriptions.

OPIOID PRESCRIBING

House Public Health – Chair: Rep. Senfronia Thompson (D-Houston)

Monitor implementation of HB 2174, which establishes limits on opioid prescribing, institutes new prescribing requirements for certain other controlled substances, and establishes continuing education requirements for prescribers.

MANAGED CARE ORGANIZATION OVERSIGHT

House Appropriations, Article II – Chair: Rep. Sarah Davis (R-West University Place)

Receive testimony from the HHSC Office of the Inspector General and monitor the contracted relationship between the State of Texas and its network of managed care organizations.

REAUTHORIZATION OF THE TEXAS MEDICAL BOARD

House Public Health – Chair: Rep. Senfronia Thompson (D-Houston)

Monitor implementation of HB 1504, which continues the Texas Medical Board until September 1, 2031. Review and identify any challenges related to the processing of complaints, including due process concerns and the independence of the Board.

REIMBURSEMENT FOR TELEMEDICAL AND TELEHEALTH SERVICES

House Public Health – Chair: Rep. Senfronia Thompson (D-Houston)

Monitor implementation of SB 670, which ensures reimbursement of telemedicine and telehealth services and expands the number of facilities eligible to receive reimbursement for those services.

ACA CONTINGENCY PLANNING

House Insurance – Chair: Rep. Eddie Lucio III (D-Brownsville)

Study ways to foster a competitive market and reduce the uninsured rate, including by exploring flexibility available through federal waivers. Study the impact to health care systems if the Affordable Care Act is ruled unconstitutional, including identifying which mandates, consumer protections, and subsidies will be lost, and which have equivalents in state law.

CONTAINING HEALTH CARE COSTS

Senate Health & Human Services – Chair: Sen. Lois Kolkhorst (R-Brenham)

Senate Business & Commerce – Chair: Sen. Kelly Hancock (R-North Richland Hills)

Study the cost of health care in Texas and make recommendations to increase access to affordable quality health care. Study ways to increase consumer health care options, provide flexibility in the market, and decrease the uninsured rate in Texas, including 1115 and 1332 waivers.

FEDERAL HEALTHCARE "FUNDING REVIEW

House Public Health – Chair: Rep. Senfronia Thompson (D-Houston)

House Human Services – Chair: Rep. James Frank (R-Wichita Falls)

House Appropriations, Article II – Chair: Rep. Sarah Davis (R-West University Place)

Review how Texas is preparing for federal budgetary changes that impact the state's health programs, including: the next phase of the 1115 Healthcare Transformation and Quality Improvement Program Waiver; Texas' Targeted Opioid Response Grant; and the Centers for Medicare and Medicaid Services proposed Medicaid Fiscal Accountability rule.

HOSPITAL FUNDING

House Appropriations, Article II – Chair: Rep. Sarah Davis (R-West University Place)

Review the ability of hospital finance methods, including trauma funding, graduate medical education payments, and supplemental payment programs, to support Texas hospitals (including rural and children's hospitals), and the potential impact from state and federal budgetary changes.

CONSCIENCE PROTECTIONS FOR PROFESSIONALS

Senate State Affairs – Chair: Senator Bryan Hughes (R-Mineola)

Assess current legal protections in Texas law for professionals and students studying to pursue a professional license that have a conscience-based objection that could interfere with a professional service. Evaluate any discrimination by state agencies against an applicant for or holder of an occupational license based on a sincerely held religious belief. Make recommendations to protect Texas professionals with conscience objections.

The complete listing of House interim committee charges issued by House Speaker Dennis Bonnen can be accessed here: https://house.texas.gov/_media/pdf/interim-charges-86th.pdf

The complete listing of Senate interim committee charges issued by Lt. Governor Dan Patrick can be accessed here: https://www.ltgov.state.tx.us/wp-content/uploads/2019/10/2019-Interim-Legislative-Charges.pdf

If you have a specific interest in any of these topics or wish to provide testimony before the House or Senate committees, please contact our lead TNS lobbyist, Tom Holloway at (512) 923-5944 or tom@crossoakgroup.com.

TNS Advocacy Report

Power of Advocacy Reflected in Final Medicare Fee Schedule

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

Last fall, the Centers for Medicare & Medicaid Services (CMS) published its final Medicare Fee Schedule for 2020. The results demonstrate the power of the AAN's comprehensive, award-winning advocacy to increase evaluation and management (E/M) payment levels for neurologic services. We also put extensive effort into mitigating proposed payment reductions to long-term EEG monitoring codes through numerous meetings and a 41-page response to the overall proposed changes—which Policy & Medicine praised as a "a lengthy tour de force regulatory comment letter"—and a full-court press on CMS staff and members of Congress by our members and staff.

Regarding long-term EEG monitoring services, we took the initiative early this year to meet with CMS to explain the vital nature of these services for our patients. The AAN joined with the National Association of Epilepsy Centers, American Clinical Neurophysiology Society, and American Epilepsy Society, and advocated for several months to persuade CMS to maintain maximum reimbursement. After the agency issued its proposed rule last summer, we met with them again. We lobbied members of Congress to help apply pressure on our behalf. Despite a tremendous amount of work, we did not negate the proposed reductions as much as we would have hoped. But we did convince CMS that it undervalued EEG services in its original proposal and it will increase the rates for several of the professional component codes, helping to offset the reimbursement cuts. In fact, CMS specifically cited the AAN's comment letter as the reason they changed their mind, validating our regulatory advocacy efforts.

We were more successful on E/M, completing a long quest begun last year when we successfully dissuaded CMS from collapsing E/M levels and reducing reimbursement (work that was recognized by the American Association of Medical Society Executives with its Profiles of Excellence Award). As CMS revisited the subject this year, we again met with officials and staff and addressed our concerns in our written response to proposed changes. Consequently, in a significant victory for neurology, CMS will not collapse the payment levels for E/M visits and, in 2021, it will implement revised office E/M documentation guidelines and increased payments. We foresee that this could generate an additional $150 million annually in Medicare payments to neurologists for E/M services beginning that year.

The Academy also was effective in getting CMS to increase payment for transitional care management and to create two new codes for principal care management. And, as you can read in our complete cover story analysis, the agency addressed changes to the Quality Payment Program for 2020 and proposed a new program for 2021 that should reduce administrative burden and be more meaningful than the current MIPS system.

Please visit AAN. com for more information on the effects of the 2020 Medicare Fee Schedule and be sure to read the January AANnews® for a deeper review of changes for the 2020 MIPS reporting year.

E/M was a tremendous win. You can be proud of the amount of time and effort volunteer members and staff put into this long process, and the respect we have from CMS when we advocate on your behalf.

2020 TNS Annual Winter Conference

Chaouki Khoury, MD, MS, FAAN, FAHS, DNBPAS
TNS 2020 Winter Program Director

The Texas Neurological Society annual meeting in Austin, is an event that I look forward to year after year. It has always been a meeting with high-quality content, condensed into 2 days, with great networking opportunity. It has helped me grow professionally since I first moved to Texas in 2011.

This year, I have the privilege of planning the meeting, and I hope you find it as interesting and educational as it has always been. We will be addressing the business of Neurology and the many changes coming to your clinic pertaining to the economics of being a Neurologist in 2020. We will also be addressing some various aspects of clinical neurology:

- The challenging diagnoses that most of us see in clinic: patient with a constellation of vague and non-specific symptoms; patient with chronic migraine and medication overuse.
- Review of current therapeutics of common neurological diseases: stroke, epilepsy…
- And update on new developments in neurology: amyloidosis, autoimmune encephalitides…

We will even round things up with such interesting topics as nutritional neurology and neurology history!

Our esteemed speakers come from all parts of Texas (Austin, Dallas, and Houston) but also from great universities around the US and Canada (University of Oklahoma, University of Toronto, Johns Hopkins University, Emory University, Dartmouth College, and Washington University in St. Louis). We designed the meeting to address the needs of our membership based on the survey responses from last meeting. We hope you would continue joining us and providing valuable feedback. The Texas Neurological Society premier role among state neurological societies rests on your membership and participation, which continues to surpass any other state neurological society.

We are looking forward to seeing all of you at our upcoming meeting!

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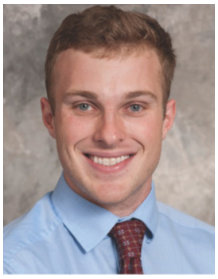

Autoimmune Encephalitis: A Review of Diagnostic and Therapeutic Considerations

Kyle Blackburn, MD
Department of Neurology and Neurotherapeutics, UT Southwestern Medical Center

INTRODUCTION

Encephalitis remains an important cause of morbidity and mortality worldwide. Recently, autoantibodies to neuronal and glial proteins have been identified in patients with new onset memory changes, seizures, and altered mental status, expanding our understanding of immune-mediated causes of encephalitis. With early recognition and treatment, many patients with autoimmune encephalitis (AE) will have dramatic improvement in symptoms and favorable outcomes. Here, we review the clinical features, evaluation, and treatment of autoimmune encephalitis, highlighting ongoing studies of immunotherapy in AE.

CLINICAL PRESENTATION

Diagnostic criteria for AE were developed by expert consensus in 2016[1]. As antibody testing is not globally available, the criteria rely primarily on clinical features and common laboratory investigations to secure the diagnosis. Symptoms attributable to AE tend to progress in a subacute manner, worsening over several days to weeks in the majority of cases. Many of the prominent clinical features of AE are attributed to involvement of the limbic structures. Difficulty with short-term memory is a commonly encountered symptom, making AE an important diagnostic consideration in the work-up of rapidly progressive dementia. New-onset seizures, commonly with temporal lobe semiology, are also frequently encountered. Patients with AE tend to have a high seizure burden, and may present with refractory or non-convulsive status epilepticus at onset. The seizure frequency typically does not appreciably change with antiepileptic medication in many cases[2]. Hyperkinetic movements, frequently with a choreiform or dystonic phenotype, may also be encountered, particularly in anti-NMDA receptor (NMDA-R) encephalitis, and may mimic tardive dyskinesias[3]. Patients with severe AE may also experience signs of autonomic instability with blood pressure and heart rate variability or central hypoventilation.

Psychiatric features, ranging from mild to severe, are also a frequently encountered symptom of AE. NMDA-R encephalitis has received significant attention from psychiatrists in recent years, as prominent psychotic features occur early in the course of illness in the absence of typical neurologic symptoms. Furthermore, the disorder commonly affects individuals in their 20s or 30s, the same timeframe that the first episode of psychosis in schizophrenia commonly manifests. Large studies have demonstrated NMDA-R antibodies in approximately 3% of patients with a first episode of psychosis, and recent efforts have attempted to identify 'red flags' for an immune-mediated psychosis[4]. While criteria have not been validated, it is generally agreed that acute psychosis with accompanying neurologic features (hyperkinetic movements, seizures, autonomic instability), early features of catatonia, and psychosis refractory to antipsychotics warrant further evaluation for AE[5, 6].

AUTOANTIBODIES AND THEIR ROLE IN AUTOIMMUNE ENCEPHALITIS

The increased recognition of AE in recent years is largely attributable to the discovery of autoantibodies that serve as a biomarker of the disorder. Generally there are two categories of antibodies, characterized by the location of their target antigen. Antibodies to intracellular antigens (e.g. anti-Hu or anti-Yo), have been recognized for several decades, and are recognized as classic causes of limbic encephalitis due to a paraneoplastic disorder. As these antibodies have no direct access to their target antigen, they are not felt to be causative, but rather indicate a T-cell mediated response to an onconeural antigen[7]. The second category comprises antibodies binding to proteins on the cell-surface. In vitro studies suggest that many cell-surface antibodies can bind to their receptor and lead to internalization and impaired synaptic transmission, supporting their role in pathogenesis of AE[8].

While antibodies provide supporting evidence of encephalitis, cases of antibody-negative AE are recognized in the literature[9]. These cases may be due by antibodies whose antigens have yet to be discovered, though a cell-mediated immune response is also plausible. Consensus criteria for AE provide criteria for probable antibody-negative AE, emphasizing the need for MRI abnormalities, intrathecal inflammation, or biopsy evidence to secure the diagnosis[1].

DIAGNOSTIC EVALUATION

The typical evaluation for AE starts with imaging. Classic limbic encephalitis results in T2 hyperintensity or post-contrast enhancement within the hippocampus and amygdala. While imaging abnormalities may lend support to an encephalitis diagnosis, it is important to note that in several common causes of AE, particularly NMDA-R encephalitis, imaging may be normal or demonstrate non-specific findings[10]. CSF studies to evaluate for signs of intrathecal inflammation (cell count, glucose, protein, oligoclonal bands) are helpful in confirming inflammation.

The differential diagnosis for encephalitis is extensive. Infectious causes represent an important consideration in possible AE, so it is prudent to submit CSF samples for endemic causes of encephalitis. In cases with temporal lobe abnormalities, a thorough evaluation for herpes simplex virus is prudent, and it is reasonable to treat a patient with

ANTIBODY	LOCATION OF EPITOPE	CLINICAL SYNDROMES	MALIGNANCY ASSOCIATION
NMDA	Cell-surface	Encephalitis with prominent psychiatric features, dyskinesias	Ovarian Teratoma
LGI-1	Cell-surface	Limbic encephalitis, faciobrachial dystonic seizures, hyponatremia	Thymoma (rare)
CASPR-2	Cell-surface	Encephalopathy, neuomyotonia, insomnia (Morvan Syndrome)	Thymoma (rare)
DPPX	Cell-surface	Encephalitis, hyperexcitability, diarrhea	Rare
AMPA	Cell-surface	Limbic encephalitis, epilepsy	Small-cell lung carcinoma
GABA-A	Cell-surface	Multifocal encephalitis, seizures	Rare
GABA-B	Cell-surface	Limbic encephalitis, epilepsy	Small-cell lung carcinoma
Glycine	Cell-surface	Progressive Encephalomyelitis with Rigidity and Myoclonus (PERM)	Rare
GAD-65	Intracellular	Encephalitis, stiff person syndrome, refractory epilepsy	Rare
ANNA-1 (Hu)	Intracellular	Limbic encepahlitis, epilepsy, paraneoplastic cerebellar degeneration, sensory neuropathy	Small-cell lung carcinoma
ANNA-2 (Ri)	Intracellular	Opsoclonus-myoclonus syndrome, paraneoplastic cerebellar degeneration	Breast, Ovarian, Small-cell lung carcinoma
ANNA-3	Intracellular	Limbic encephalitis, paraneoplastic cerebellar degeneration, neuropathy	Small-cell lung carcinoma
PCA-1 (Yo)	Intracellular	Paraneoplastic Cerebellar Degeneratin	Ovarian, Breast
PCA-2	Intracellular	Paraneoplastic cerebellar degeneration, neuropathy	Small-cell lung carcinoma
Amphiphysin	Intracellular	Limbic encephalitis, stiff person syndrome, paraneoplastic cerebellar degeneration	Breast, Small-cell lung carcinoma
CRMP5 (CV2)	Intracellular	Encephalitis, epilepsy, sensory neuropathy	Small-cell lung carcinoma, thymoma
Ma-2	Intracellular	Limbic encephalitis, cerebellar ataxia, myelitis	Testicular cancer
IgLON5	Cell-surface	Sleep disorders (parasomnias, insomnia), stridor, gait disorder, movement disorders (dystonia, chorea)	Rare
Kelch-like protein 11	Intracellular	Ataxia, hearing loss, diplopia, dysarthria, seizures	Testicular Cancer

Table 1. Antibodies associated with autoimmune encephalitis

acyclovir until HSV testing returns negative when diagnosis is unclear[1, 10]. Furthermore, public health officials have identified an increase rate of Easter Equine Encephalitis virus across the United States in 2019, though to date no cases have been reported in Texas[11]. Other mimics of AE, such as toxic/metabolic encephalopathies, prion disease, and CNS vasculitis, should be considered based upon the clinical presentation and supplementary data.

In all cases of suspected AE, submitting samples for antibody testing is recommended, as it can help secure a diagnosis and, in the case of classic paraneoplastic antibodies, prompt the clinician to perform aggressive malignancy screening. As different antibodies may cause an encephalitis with overlapping features, it is recommended to order antibody 'panels' which test for several antibodies associated with AE. Since the sensitivity for certain antibodies, such as NMDA-R antibodies, is higher in CSF, it is advised to submit both serum and CSF antibodies for testing in most circumstances[1, 10].

As AE may arise in a paraneoplastic context, a screen for malignancy is generally performed in most patients. The extent of surveillance is dictated by patient risk factors and by the presence of an antibody known to have a high association with cancer (*see Table 1*). Typical screening at the author's institution includes a CT of the chest, abdomen and pelvis to evaluate for solid tumors or enlarged lymph nodes[2]. NMDA-R encephalitis has an association with ovarian teratoma in young women, and it is recommended to pursue a transvaginal ultrasound in this demographic8. In men, antibodies to Ma/Ta and Kelch-like Protein 11 are commonly associated with testicular tumors[12, 13]. Paraneoplastic AE may be the first indicator of cancer in an individual, and may occur years before a tumor is clinically identified; thus, when an antibody with a strong association malignancy is encountered, close surveillance is advised. In these cases, a whole body PET has been shown to improve sensitivity for malignancy detection, and is recommended[14].

Continued on page 8

TREATMENT

Treatment of autoimmune encephalitis generally involves two phases. In the acute stages, treatment aims to reduce acute inflammation and remove substrate for an aberrant immune response. While clinical trials are lacking, experience suggests treatments such as IV glucocorticoids, plasma exchange, and intravenous immunoglobulins are effective and result in improvement in condition[10]. The authors generally use a combination of IV steroids and plasmapheresis for patients admitted with suspected AE. When possible, the use of objective measures such as cognitive testing or seizure frequency may help determine treatment response and inform next steps.

While AE can be monophasic, many patients are at high risk of relapse. Immuno-therapies are frequently administered following acute treatment to prevent relapse, particularly in patients with severe presentations. To date, no randomized controlled clinical trials have been published for AE. In cases of AE with antibodies to cell-surface antigens (such as NMDA-R or LGI-1 antibodies), many experts recommend immunotherapy using anti-CD20 agents such as rituximab, which target B lymphocytes[3, 10, 15]. In cases with antibodies to intracellular targets, or in suspected seronegative paraneoplastic AE cases, cyclophosphamide is preferred, given evidence that many of these cases involve simultaneous T-cell mediated autoimmunity[10, 16]. Agents commonly used to treat other neurologic autoimmune diseases, with as mycophenolate and azathioprine, have also been reported to prevent worsening in published case reports.

A randomized placebo-controlled clinical trial exploring the role of ocrelizumab in preventing worsening in AE is underway at UT Southwestern under the direction of Dr. Steven Vernino. This trial and future multicenter randomized controlled clinical trials will be critically important to establishing long term efficacy and safety of immunotherapies in AE.

As there are no validated measures to determine risk of relapse, close follow-up and monitoring is advised in all AE cases. Symptoms that may indicate a relapse frequently include the return of frequent seizure activity, worsening memory difficulties, or worsening psychosis. In antibody associated cases with pathognomonic findings such as faciobrachial dystonic seizures for LGI-1 antibodies or diarrhea for DPPX antibodies are also an important clue that a patient is experiencing a relapse. Similar to the initial presentation, symptoms typically worsen over the course of several days.

Recovery from AE has not been systemically studied. In milder cases, patients may experience return to baseline function. Many patients with AE recover well but report residual issues with concentration, behavior, and memory[17]. The subtype of AE likely has an impact on expected outcomes and recovery. Patients with NMDAR antibody AE typically experience a very slow recovery of symptoms, often taking many months to achieve meaningful improvement in symptoms. Certain clinical variables, such as a robust response to first line treatment, are predictive of good function at one year[3].

CONCLUSIONS

The diagnostic approach to encephalitis is complex, but prompt identification of AE and institution of immunotherapy can result in favorable outcomes. Autoantibody testing and malignancy screening is recommended in all cases of suspected AE. An exploratory clinical trial in Texas is exploring the role of immunotherapy in preventing worsening in patients with antibody-positive AE, and further trials are anticipated in the future. Other future directions for the study of AE include quantitative measurements of long-term outcomes and efforts aimed at improving recovery from AE.

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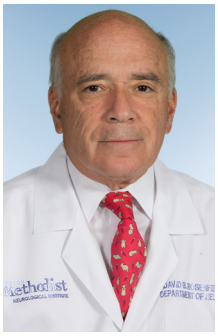

The Puzzle of the Midline

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It is a pleasure to watch your child neurologically develop. When my outstretched arms elevated overhead our newly born son, introducing him to a non-embryonic world, I was amazed as he kept his face forward, laterally extended both of his arms with pointed index fingers and proceeded slowly to bring them together toward the midline. I could not help but query whether this less than hour-old baby was unifying and solidifying both halves of his universe or whether, instead, his movements merely reflected serendipity.

To be fair to my initial midline perspective, many posit that young babies place their feet in their mouths to instruct the nascent somatosensory systems the length of their limbs so that they can more readily learn individual physical parameters and constraints. These young brains have many ways of teaching the organism what they are and what they are not as their cerebrum internally connects and myelinates its visual, auditory and somesthetic pathways, moving along the developmental continuum.

Within this framework of development, that same young child soon learned to offer people something, anything, that he held in his hand, firmly expecting them to take it and possibly affirm to himself how to control other beings as well as his own space in the universe. One day, I held him in front of a mirror and he reached toward his image, offering his mirrored doppelgänger the morsel in his hand but burst into tears when his compatriot stared back, similarly crying but not taking the object my son was offering.

He then fooled around in front of the mirror, stared at the image and again began crying. The child seemed to recognize that the mirror image was he, but did not fathom that there was only one of him. He, alone, stood as one in the world and no matter how much someone else might look like him, wear his clothes or mirror his image and movements, he now had to learn that there was no other true self. The boy who looked and acted like him did not take the food and seemed to offer his own, perhaps creating our son's first sordid rejection which, unfortunately, emanated from himself.

All brains have to learn these seemingly simple yet complex processes: we are individually unique and are ourselves, no one else. Concordant with this uniqueness, our brains probably have not changed much over the past few millennia, perhaps even longer, causing one to wonder why the brain of the Roman citizen who for entertainment watched people be devoured alive, concurrently functioned so differently from the brains of

others during that same time period who did not want a cow to experience pain when brought to slaughter.

How is it that brains do this, some opting for carnivorous entertainment and others protecting a non-human, non-primate bovine? How do brains approximate, intercalate or prevaricate their cerebral semi-lunes of existence?

Apposition of two pointed fingers in the midline may juxtapose two halves of an external environment but different brains proceed at different times to mete out varying equations of what are those external environs, ranging from Romans of yesteryear to the noblesse and warriors of today. How a brain then saw the ancient world or digests the current one may be the same on a Hubert and Wiesel cellular level but how that brain interprets this visual input (or any other input) is seldom isomorphic with its peers.

Some brains view a triangle and produce a Pythagorean theorem while others posit how to build catapults to storm cities, wage war or wage peace. Some watch the lions, some cherish the cows and some even become neurologists and neuroscientists.

We neurologists pretty much recognize that human beings are much the same on the inside but these humans vastly perceive and thus do different things with, on and to the outside. How we reflect, distill and cogitate our neural inputs adds from each of us a piece to the ongoing jigsaw puzzle of the world, whether we work that puzzle from the inside out or the outside in.

There is only one midline of anything but where one starts the journey toward that midline and how one arrives reflects the road taken. In the end, everything has to blend or the puzzle remains incomplete.

In some ways, that is pretty much what we in the neurology community do: try to ascertain how the micro- and macroscopic pieces of the cerebral puzzle conjoin and fit, and what happens when a piece becomes missing or is broken. Maybe, one day, some of these pieces can be replaced or fully repaired or, perhaps, we might even be able to build a new puzzle.

Cerebral Palsy?

Bernard M . Patten, MD, FACP, FRSM, FTNS, FAAN

PATIENT RICHARD

His mother wheeled him into clinic. She is an administrator of a hospital in a suburb of Dallas. She heard about a woman who recovered from paralysis of her legs and hoped her son, Richard, could also be helped.

Richard was the result of a normal pregnancy and delivery, but he never hit mental and physical milestones on time so he was considered, by the definition of the era, mentally retarded.

Despite handicaps he worked full time as a stocking clerk in a supermarket until a year prior to the clinic visit when, at age 17, his thinking got worse and he became unable to walk or work. His mother consulted three neurologists who each told her Richard had cerebral palsy and there was nothing to do. Their quote according to Mom: "There is no treatment for cerebral palsy."

On examination Richard was a mess with signs and symptoms of nervous system disease at every level of the neuraxis. He was demented. He drooled. He could speak only grunts and moans. His legs and arms were weak, spastic, ataxic, he had the shakes, etc..

Mom: "I thought cerebral palsy was static. Not progressive. Richard started getting much worse at age 10 and continued to worsen until last year when he fell apart."

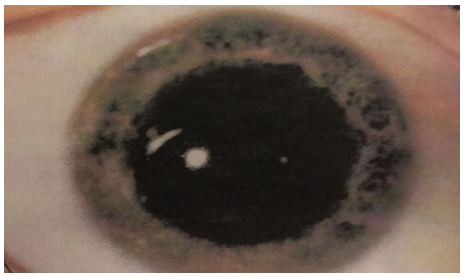
Attention: At this point what would you tell Mom about her belief that cerebral palsy is static? Pause to consider and formulate your answer and then compare your answer with what she was told.

Neurologist: "That's correct."

Mom: "What's correct?"

Neurologist: "Cerebral palsy does not worsen. It is static and never progresses."

Mom: "So how do you explain Richard getting worse?"



Neurologist: "Either he had cerebral palsy and something else came along to make him sicker or he never had cerebral palsy and he had and now has that same something else making him sick and sicker."

Mom: "The other thing that bothers me is his blue eyes turned brown."

Neurologist: "Blue eyes turned brown?"

Mom: "He used to have such beautiful blue eyes and now they are brown."

Neurologist: "Wow! Holy Cow! That's great! I missed the eye thing. Better have another look."

Take a good look at Richard's eye. Tell what you see and reach a conclusion about what's the diagnosis.

Neurologist: "Bingo! We have a diagnosis. I missed something really important.

Richard's eyes are blue but at the edge (the limbus) of the cornea there is a yellow-brown, copper-colored granular deposit on Descemet's membrane makes his eyes appear brown. This is none other than the famous Kayser-Fleischer ring, the best known sign of Wilson's disease, a condition caused by a defect in copper metabolism. The ring was visible with the naked eye but looked even more impressive with the ophthalmoscope set to a +40 lens. This copper containing ring is present in every patient with neurological problems due to Wilson's disease and most patients with Wilson's disease. The ring is usually most dense, and first visible, at the upper and lower poles of the eye. When fully developed, such rings go all around just as they did in Richard. The rings will begin to disappear after kidney transplant and after the induction of negative copper balance by penicillamine. Usually, fading will simply reduce in the reverse of the pattern of development, so the lateral margins of the cornea will lose their copper first, followed by the superior and inferior poles. The rings completely disappear in some patients undergoing therapy.

This is great! We are going to make Richard's brown eyes blue and in the process his situation will be improved."

At this point the neurologist started crying. He wished he could stop crying over cases like this. It looks unprofessional.

All choked up he had trouble telling Mom what follows.

Neurologist: "Richard suffers from a rare disease of copper metabolism. The defect is present in every cell of his body and it causes copper to build up in excessive amounts. Neurological symptoms are unusual before age 12, probably because insufficient copper has accumulated in the brain, but can occur. I know Richard has a copper problem because I can see the copper build up in the cornea of his eyes. That's why his blue eyes seemed to have turned brown. His eyes are still blue, but the blue color is hiding behind the brown copper."

Now Mom is smiling and then she cries too.

Richard was admitted to the Hospital for diagnosis and treatment. The characteristic laboratory feature of the disease is a low or absent serum ceruloplasmin, the blood protein that carries copper in normal people. Normal adults have a value between 200 and 400 milligrams per liter. The absent protein is not the cause of copper accumulation. It is just a marker of the defect. Richard's ceruloplasmin was reported by the laboratory at 325, a normal value.

Oh no! The lab test fails to confirm the clinical diagnosis

Ugh! What do you do now?

The most important laboratory test used to confirm the clinical diagnosis of Wilson's disease is normal. Are we up the creek in a canoe without a paddle? How is his Mom going to take the bad news when her hopes have been built up so much?

LESSON: CLINICAL DIAGNOSIS IS ALWAYS MORE IMPORTANT THAN ANY TEST.

Measurement of copper and copper pro-

teins is a science, and a laboratory that does this determination should be thoroughly equipped to do it properly. Clinically this patient has severe Wilson's disease and yet the laboratory has reported a normal value for the blood protein usually deficient in the disease. What should we do about that? Which is correct: The laboratory value that says Richard doesn't have absent ceruloplasmin or our clinical diagnosis of Wilson's Disease based on what we actually see in his cornea?

What would you do to resolve this dilemma? What is the more trustworthy evidence: the lab result or the clinical picture?

Think about what you would do. Repeat the test? Go to the lab to interview the technician? Accept the normal value as a fact? Look up the literature to see if you can have Wilson's Disease with a normal ceruloplasmin level? What?

Answer: Yes, the literature does mention cases of Wilson's Disease with a normal ceruloplasmin level, but one wonders if the laboratory that did the test in those cases did it correctly. Anyway, no harm in checking things. We should march down to the laboratory and talk with the technician who did the test to find out what's what.

> Lab Director: "What's up?"
>
> Neurologist: "I have a patient with Wilson's Disease and your lab reported a normal value for ceruloplasmin. That has to be an error so let's find out what happened."
>
> Director to the technician: "Let's see you repeat the test."

Re-examination of the same specimen under supervision showed no detectable ceruloplasmin. Zero! Richard has no ceruloplasmin in his blood. The clinical diagnosis is supported, probably confirmed.

WHAT HAPPENED:

When the technician did the test originally, she got a zero value also. She felt she had made an error in running the test and therefore she proceeded to enter a normal value in her report. As this case illustrates, absolute honesty and scientific integrity in the laboratory are vital to proper diagnosis of Wilson's Disease or any other disease. So what should be done with the technician who reported a false laboratory result? What would you do, dear reader?

The technician was fired of course.

OTHER LAB RESULTS CONFIRM THE DIAGNOSIS:

Richard's urine copper was sky high 1200 micrograms per 24 hours. Normal is less than 40. His urine copper excretion increased to 3600 micrograms per 24 hours when he got penicillamine. The penicillamine is an agent that binds copper and helps excrete copper in the urine. No normal person excretes that amount of copper after penicillamine so the diagnosis of Wilson's Disease is amply confirmed and the effectiveness of penicillamine as a treatment to remove copper in Richard's case is proved.

In over 900 papers on Wilson's Disease reviewed[1] show no double-blind prospective controlled study comparing the effectiveness of actual treatment and placebo. Nevertheless, there is overwhelming consensus among neurologists that conventional treatments for Wilson's Disease are highly effective. Thus, if a treatment really works, you don't need statistical analysis or a big expensive clinical trial to prove it works. Many of the currently available medicines are only marginally effective because the test to prove they are effective involves only a statistical proof. Really effective treatments like L-DOPA for Parkinson's disease or penicillin for pneumonia needed no massive prospective randomized (and expensive) clinical trials to prove they work. Observing the effect on individual patients can be and should be evidence enough.

TREATMENT:

Because the fundamental problem in Wilson's Disease is excessive accumulation of copper in tissues, treatment should also consist in decreasing copper intake. Copper intake is decreased by administering a low copper diet. So Mom got educated about the copper content of foods and warned to avoid those with the highest copper content like nuts, chocolate, coffee, and lobster.

Sorry about lobster. Lobster blood is copper based unlike human blood which is iron based. So, no lobster for Richard.

Potassium iodide 20 milligram four times daily binds copper and thereby decreases absorption by creating copper iodide which is excreted in the stool. Zinc supplements induce metallothioneins that also decrease copper absorption.

RESULT

Richard problems with blood, liver, kidney, and brain reversed or improved and he returned to work. Mom was pleased as punch with the improvements. And yes, his brown eyes turned blue.

DISCUSSION

About trace metals: Copper is essential to human health, because it is a component of many essential enzyme systems including cytochrome C oxidase, superoxide dismutase, tyrosinase, and dopamine beta hydroxylase. But copper is toxic when present in above normal amounts as it is in Wilson's Disease.

Other essential metals are manganese, vanadium, iron, molybdenum, cobalt, zinc, and chromium. Each is at the center of an enzyme system and each probably has a specific transport protein and a specific regulatory pathway for excretion in the bile. Knowing how human disease works its havocs, it is reasonable to conclude that there is at least one disease caused by the excess of each of these metals and one disease caused by a deficiency of each of these metals. The reason we don't know more about such diseases is that funds for basic research on them were cut off in the 1960s in order to pay for the trip to the moon.[2]

The presence of a metallic ion in the center of an enzyme system is a consequence of the evolutionary history of life on this planet. Indeed, the first enzymes were the trace metals themselves, which are able to lower energy barriers, thereby facilitating electron transfer and chemical reactions. Subsequently, in the course of evolution, pyrole groups were engrafted around trace elements, and last, proteins were attached to the pyroles. Thus, it is no accident the usual enzyme structure consists of a metal surrounded by pyroles and a protein.

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Zahari Tchopev, MD

Functional Recovery of an Active Duty Soldier after Anoxic Brain Injury with Marked Diffusion Restriction

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INTRODUCTION

The reported annual incidence of out-of-hospital cardiac arrest in the United States is 326,200. Of those, the survival rate to hospital discharge is 10.6% for any recorded rhythm, while the reported survival with good neurologic function is only 8.3% for adults.[1] Among patients who survive cardiac arrest, prediction of the neurological outcome is an important, but difficult responsibility of the patient's care team. This prognostication sets expectations for the patient's family regarding the patient's long-term quality of life if they survive.[2] In particular clinical neurologists or neurocritical care physicians are often consulted to aid in prognostic evaluation.

Multiple studies have suggested various combinations of prognostic factors such as a neurological assessment, electroencephalography, evoked potentials, imaging, and serum levels of brain-specific markers, however many have shown high false positive rates.[3,4] This may risk the chance of the "self-fulfilling prophecy" effect, in which a poor prognostication is used as justification to withdraw care.[5,6] Modern, advanced neuroimaging is a tool that has gained utility in clinical decision making. Namely, diffusion magnetic resonance imaging (MRI) has consistently reported robust associations with functional outcomes in these patients, while functional MRI (fMRI) is further being explored as a clinical prognostication tool. Specifically, the detection of diffusion restriction in the basal ganglia, thalami, cerebellum or cortex using MRI diffusion weighted imaging (MR-DWI) has been associated with poor neurologic outcome with high sensitivity and positive predictive value, and is also suggested to be less subject to the effects of ongoing medical management.[7,8]

CASE PRESENTATION

A nineteen-year-old previously healthy active duty male with no familial or personal cardiac history suffered a witnessed, out-of-hospital ventricular fibrillation cardiac arrest during a fitness activity. He received bystander cardiopulmonary resuscitation (CPR) for an undocumented time followed by twenty minutes of emergency responder CPR with three defibrillation attempts prior to return of spontaneous circulation. He was intubated in the field and upon arrival to an outside hospital, he was found to be in normal sinus rhythm, and lab work up revealed elevated creatinine kinase (peak 3555 IU/L; ref. 30 – 200 IU/L) and lactic acid (peak 7.4 mmol/L; ref. 0.7 – 2.1 mmol/L), which peaked and down trended acutely, with a negative urine drug screen. A chest x-ray and head computed tomography in the emergency department were both unremarkable. He underwent a 24-hour therapeutic hypothermia protocol. His rewarming course was complicated by multifocal myoclonus and continued unresponsiveness.

On day four post-resuscitation, he was transferred to our tertiary, multi-specialty facility for continued post-resuscitative care and evaluation. On arrival to our facility, the patient remained comatose with episodes of extensor posturing and myoclonus involving the face and bilateral lower extremities. He had intact brainstem reflexes, hyperreflexia of the lower extremities, and bilateral Babinski signs. A 21-channel digital EEG of thirty-two minutes duration demonstrated monomorphic, nonreactive alpha activity, consistent with alpha coma along with intermittent, generalized, rhythmic delta activity (**Figure 1**). MRI of the brain on day five showed diffusion restriction involving the bilateral frontal, parietal, and occipital lobes as well as T2 hyperintensity of the bilateral basal ganglia, right greater than left, and specifically involving the caudate nuclei and right lentiform nucleus (**Figure 2**). Continuous EEG monitoring later identified intermittent reactivity to stimulation with bursts of delta activity. The patient underwent tracheostomy and PEG tube placement on day nine. After 18 days he regained consciousness and began following simple commands. Prior to discharge, the patient was awake, conversational, and ambulatory with a walker. After six weeks of intensive neurorehabilitation, his tracheostomy and PEG were reversed. A cardiac evaluation to include stress cardiac magnetic resonance imaging (CMRI), transthoracic echocardiogram and genetic cardiac work-up were negative. No formal coronary angiogram was performed, however coronary origins were adequately visualized on CMRI. A subcutaneous implantable cardioverter-defibrillator (S-ICD) was implanted to prevent another episode of sudden cardiac death. At three month follow-up, he was able to function independently with the only subtle left ataxic hemiparesis, minimal imbalance and mild amnesia, indicating a good outcome.

DISCUSSION

One of the leading causes of coma is anoxic ischemic encephalopathy following cardiac arrest.[9] Improved practices in continuous CPR, care in intensive care units and TTM may contribute to increased rates of initial survival, and survival to discharge.[10] Consequently, the prognostication of these patients is of particular interest to patients, family and physicians.[1,11] Providers, and particularly neurologists, examine the unresponsive patient to confirm the diagnosis of coma, yet also to help differentiate between the other stuporous states such as persistent vegetative state, minimal consciousness state and brain death. The anatomical cause of coma is attributed to any one of three areas of the brain, to include the brainstem reticular activating system (RAS), bilateral frontal lobes, and bilateral temporal lobes.[12] In the post-TTM era, absent brainstem reflexes (namely pupillary light response and corneal reflex), absent or extensor motor responses to pain, and the presence of myoclonus particularly in the first 72 hours, accurately predict poor outcome.[13,14] Clinical exam findings face criticism however, because they are clinically used for decision making yet simultaneously act as cohort study criteria, thus raising concern for selection and channeling bias.[2,6] To aid the physical exam, EEG is widely available and has been used

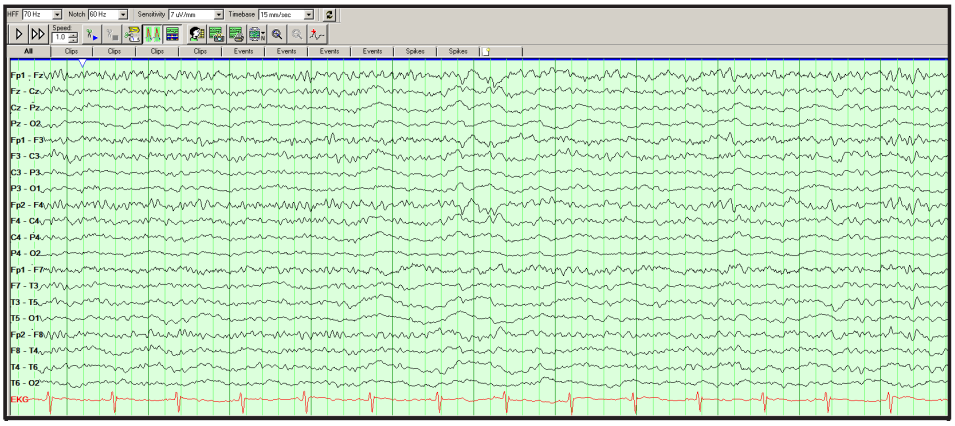

Fig. 1. 21-channel digital EEG obtained 4 days after cardiac arrest consistent with alpha coma.

for decades as a prognostication tool, and has also been verified as powerful tool in the post TTM paradigm.[2,15] Particularly strongly associated with poor outcome, is myoclonic status epilepticus.[13] Another electrophysiologic tool is early-latency somatosensory evoked potentials (EP), which can play a role in prognostication, but have mixed additive utility when used alongside EEG.[2] A collective criticism of the physical exam and electrophysiology studies is the confounding factor of concomitant medical treatment, particularly with sedatives, thus leaving interpretation of findings more difficult.[5,16,17]

Biomarkers of neuronal injury and advanced brain imaging have drawn increased interest as prognostic markers. The most studied markers include neuron-specific enolase (NSE) and S-100 β, which do correlate with other prognostication measures as well as poor outcome. However, studies are variable, with low positive predictive value, and biochemical sources of these are not mutually exclusive to brain tissue nor have they been well studied in the TTM era, and thus are cautioned against using alone.[2,3,6] Finally, neuroimaging with MRI has grown in interest as a prognostic tool. The DWI modality is an exquisitely sensitive option to visualize hypoxic-ischemic injury after cardiac arrest, and far superior to CT.[18] It's currently recommended that MRI be done between 24-48 hours and 7 days after a cardiac arrest.[19] Using this modality, studies have shown that when the brain regions outlined above show diffusion restriction, especially in multiple areas, it allows for reliable prediction of poor neurologic outcome in comatose patients, even those treated with TTM after cardiac arrest.[2,7] Further, diffusion MRI can be used to quantify global brain damage from ischemia by averaging diffusion restriction.[19,20] However, the absence of these findings is not a reliable predictor of a good outcome.[7]

This comatose cardiac arrest patient status post TTM had multiple findings to include a prolonged coma, early multifocal myoclonus, EEG findings consistent with alpha coma and marked restriction diffusion on multiple areas of the brain, which are typically associated with poor outcomes. Despite these findings, the patient emerged from his coma, and had good functional recovery at three month follow-up. Factors that may have contributed to this patient's recovery despite the poor prognostic signs and anoxic ischemia might include his relatively young age, TTM, and early, high-quality CPR. This represents a practice pearl for Neurologists who are asked to provide prognosis in anoxic brain injury. In our practice we continue to use the evidenced-based physical examination, electrophysiology, and imaging findings to help inform prognosis in anoxic brain injury. We continue to struggle on how to use and interpret serum biomarkers in the post-TTM era. However, it is equally important to consider if individual patients match the cohort characteristics that were studied before making a prognostic evaluation and contributing to the "self-fulfilling prophecy." Those factors may include but are not limited to age, etiology, image and study timing, concomitant medical therapy, duration of cardiac death or institution of TTM.

1) Drs. Tchopev, Elsbernd and Koehn all met the ICMJE recommended authorship criteria: contributed substantially to the conception, acquisition, interpretation and care of the patient, drafting and revising the work, giving final approval of the version to be published and, agree to be accountable for all aspects of the work in ensuring accuracy and integrity.

2) Drs. Tchopev, Elsbernd and Koenig have no conflicts of interests regarding this submission.

3) The views expressed herein are those of the authors and do not reflect the official policy or position of Brooke Army Medical Center, the U.S. Army Medical Department, the U.S. Army Office of the Surgeon General, the Department of the Army, the Department of the Air Force and Department of Defense or the U.S. Government.

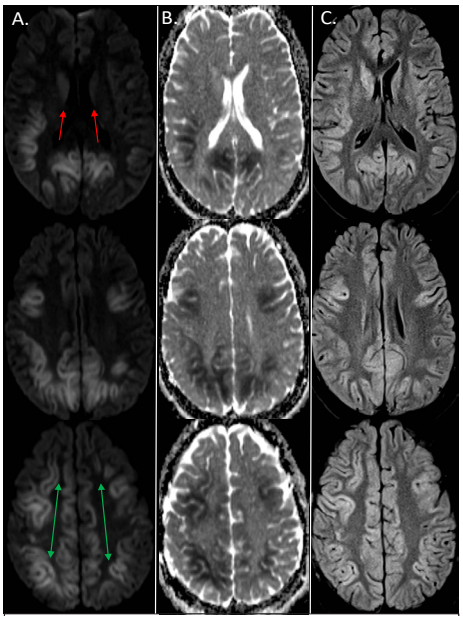

Fig. 2. Axial slices of DWI (A.), ADC (B.) and T2 FLAIR (C.) MRI correlated sequences obtained 5 days after cardiac arrest, demonstrating bilateral (right greater than left) T2 hypertensities of the basal ganglia (red arrows), as well as diffusion restriction of the parietal, occipital and frontal cortices (green arrows).

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Sidra Saleem, MD

Amyotrophic Lateral Sclerosis With C9orf72 Mutation, Literature Review And Cases Analysis

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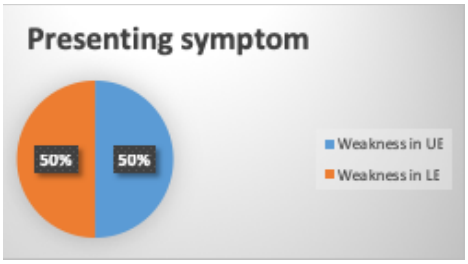


INTRODUCTION

Amyotrophic lateral sclerosis (ALS) also called Lou Gehrig's dissease is a progressive degenerative disease of motor neurons. The disease usually present with either limb onset which is 80% of cases and about 20% with bulbar onset.[1] In limb onset ALS, patients usually present with distal weakness in upper or lower extremities. Bulbar onset presents with dysarthria and dysphagia. Either of these typically would progress to involve both limbs and bulbar muscles.

ALS prevalence in the US is 5 per 100,000 people in 2014, similar to that reported in 2013.[2] Most of the cases of ALS are sporadic but 5-10% are familial (fALS) with mendelian inheritance.[3]

Several mutations have been found to cause ALS, namely superoxide dismutase 1 (SOD1), TAR DNA binding protein (TARDBP), angiogenin (ANG), fused in sarcoma (FUS), optineurin (OPTN), and chromosome 9 open reading frame 72 (C9ORF72).[4]

The mutation found in the C9ORF72 (C9) gene is characterized by an expanded GGGGCC (G4C2) hexanucleotide repeat expansion (HRE) in its non-coding region on chromosome 9p21. This mutation represents the most common genetic abnormality in frontotemporal dementia 10–30% and amyotrophic lateral sclerosis 20–50%. (Starr et al 2018)

Chromosome 9 open reading frame 72 is required for the normal function of myeloid cells, and altered microglial function may contribute to neurodegeneration in *C9orf72* expansion carriers.[5] This mutation is not only found in patients of ALS but also in patients of Frontotemporal dementia (FTD). This overlapping molecular pathology of ALS/FTD opens many clinical aspects.[6]

According to Choi et al 2018 *C9ORF72* hexanucleotide repeat expansions have been found in 6.7% of all ALS cases making it the commonest mutation in ALS.

How ALS patients with and without C9orf72 mutations differ clinically? Is there a clinical heterogeneity among those with the mutation? We will present 4 patients with the mutation and compare them with patients without the mutation.

PATIENTS, METHODS, AND EVALUATION

Four symptomatic patients were seen by neuromuscular specialist between July 2017 and December 2018 at the the Nerve and Muscle Centre of Texas in Houston, Texas. The epidemiological data of the patients are summarized in Table 1. Clinical data were collected by a combined approach of our team. Neurological examination, genetic testing, nerve conduction studies and electromyographies were conducted in our center.

RESULTS

Of the 4 cases presented during July 2017 to December 2018, 75% (3/4) were male and 25% (1/4) was female. 75% (3/4) cases were presented in their 50s and 25% (1/4) in his 60s. All patients were having positive family history. (Graph 1)

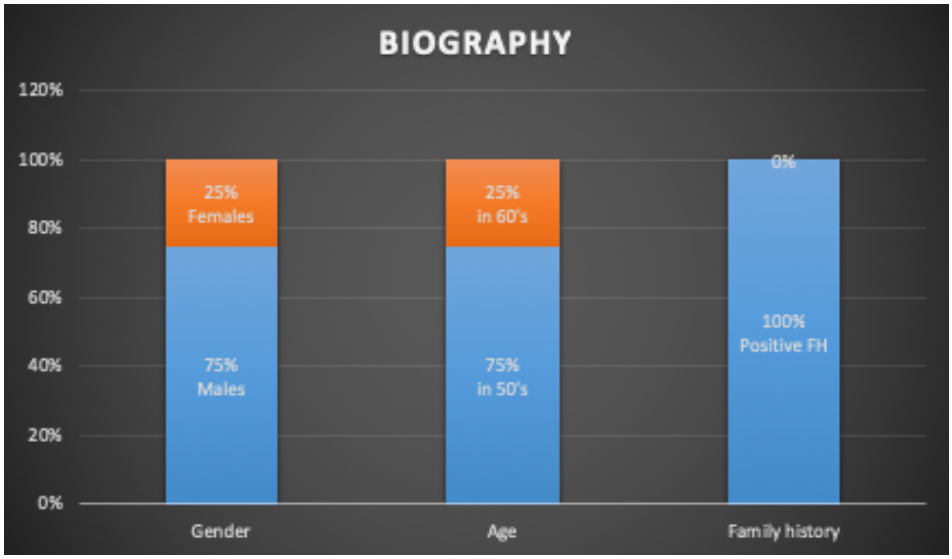
PRESENTATION AND EXAM FINDINGS

Among all patients, half (2/4) of patients presented with the weakness in upper extremity (UE) and half (2/4) patients presented with weakness in lower extremity (LE) and foot drop. Weakness was painless and progressive. They all were having muscle cramps, muscle weakness, stiffness and loss of muscle mass in involved regions.

On examination, all patients were having both upper motor (UMN) and lower motor (LMN) signs. UMN signs were exaggerated reflexes in all patients in the involved nerve supply and LMN signs were fasciculation and atrophy. Proximal muscle weakness was present in 75% (3/4) patients. None but 1 patient was having sensory involvement of posterior tract. 25% (1/4) patient was presented with the involvement of bulbar neurons (symptoms of dysarthria and dysphagia).Cerebellar exam, cognition and memory was normal in all patients.

Diagnosis of ALS in all patients was done by using El Escorial Criteria (Degeneration of UMN, LMN, spreading of symptoms, absence of other diagnosis). EMG and NCV was done to confirm denervation and it's distribution. In all patients, diffuse denervation with no sensory changes and low motor amplitude confirmed motor neuron disease.

Genetic testing was done to confirm the mutation of C9orf72 and rule out other mu-



tation, using genomic DNA obtained from blood, repeat analysis was performed via the Asuragan AmplideX PCRJCE C9orf72 kit. The sample was evaluated by repeat-primed FCR to identify expanded alleles as well as determine the number of repeats in alleles with fewer than 145 repeats. Nucleotide repeat numbers up to 25 are reported with an accuracy of +/- I repeat and repeat numbers greater than 25 ae reported with an accuracy of +/- 3 repeats. Internal standards were analyzed along with clinical samples to evaluate assay performance. All of our patients were heterozygotes of repeat expansion of G4C2 with 1 allele of greater than 145 repeats and 1 allele of less than 25 repeats. All other mutations were negative.

Spirometry was performed to see the respiratory muscles involvement. 25% (1/4) patient was having low vital capacity. Rest of the patients were having normal findings.

	Pt 1	Pt 2	Pt 3	Pt 4
Presenting sx	Muscle weakness, LE	Muscle weakness, UE	Muscle weakness, LE	Muscle weakness, UE
UMN signs	Yes-in LE (exaggerated reflexes)	Yes- in UE (exaggerated reflexes)	Yes- in LE (exaggerated reflexes)	Yes- in UE (exaggerated reflexes)
LMN signs	Yes- in LE (muscle atrophy, fasciculation)	Yes- in UE (fasciculation)	Yes- in LE (muscle atrophy)	Yes- in UE (muscle atrophy)
Bulbar signs	No	No	No	Yes
Eye/Hearing involvement	No	No	No	No
Proximal weakness	Yes- Difficulty is rising from chair, climbing upstairs	No	Yes- Difficulty is rising from chair, climbing upstairs	Yes- Difficulty is rising from chair
Sensory findings	Normal	Normal	Normal	Decreased sensation to PP, vibration, and proprioception in the feet up to the shins
Cerebellar signs	No	No	No	No

Table 1

DISCUSSION

Expansion in chromosome 9 has detrimental effect on the function of the motor neuron. Dysfunction of the synapse is one concept which occur due to the overexpression of poly-GA dipeptide repeat (DPR) proteins in primary mouse cortical neuron cultures led to decreased dendritic arborization, caused by the co-aggregation of the transport factor Unc119. (Starr et al 2018)

Excitotoxicity is another way the motor neuron get injured in C9 ALS. According to Selvaraj et al their study showed that C9 mutation leads to increased mRNA and protein expression of the GluA1 subunit of AMPA receptors concomitant with increased Ca2+ permeability of C9 iPSC motor neurons. Increased Ca2+ permeability and increased susceptibility to AMPA-mediated cell death is due to an increase in GluA2 lacking AMPA receptors. (Selvaraj et al., 2018).

Alteration in neuronal excitability has also been studied in ALS patients with the C9 mutation. Hyperexcitability in neurons is when the neuron has lower threshold for firing action potential and is more excitable than usual and more frequently. Alterations in evoked junctional potentials means an impaired neurotransmitter release at the neuromuscular junction and overexpression of poly-GR DPRs suppresses both spontaneous and evoked responses (Zhang et al., 2015)

ALS patients with pathological expansions in C9ORF72 have a heterogeneous presentation in general, and most are indistinguishable from ALS with no C9ORF72 mutation based on symptoms alone (Knock et al 2012).

However, certain features appear to be more common, such as earlier age of onset, family history, and rapid progression in some cases (Knock et al, boeve et al)[7]. In our cohort, the mean age of presentation was 54.8, which is in line with the earlier age of onset of 57.3 years found in literature. (knock et al, Sgobbi et al)[8]. In addition, all patients in our cohort had a positive family history of ALS in first or second degree relatives (table 1).

As expected, our cohort presented in a similar fashion to ALS as reported in the literature, with a 50% having UE or LE involvement first. In addition, patients 1-3 did not progress rapidly since presentation and did not have bulbar symptoms. Patient 4 initially presented with UE weakness, and within 7 months developed dysarthria, excessive drooling, and dyspnea requiring BiPAP. The difference in progression between these patients is not accounted for by their specific mutations, as all were heterozygous and had more than 145 repeats in one C9ORF72 allele. Studies have also shown that different repeat sizes do not predict severity of progression of ALS (Dols-Icardo et al)[9]. FTD was not investigated in these patients yet, but no signs of dementia were seen clinically. Overall, our patient cohort shares some characteristics that are found in familial ALS as is seen in the age of onset and family history. Further studies for this cohort include monitoring for signs of dementia and investigating whether FTD is prevalent in these patient's families, and monitoring the progression and severity of disease.

CONCLUSION

C9orf72 is one of the most important cause of ALS that present early and progress rapidly. Positive family history is present in all cases. FTD may or may not be present. With early diagnosis of these patients, we can provide and prepare them for disease progression.

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What is Cluster Headache?

Britt Talley Daniel, MD

Cluster headache is the most severe headache known to man. It is called "suicide headaches" for good reason. It is interesting that when the first American classification of headache was released in the JAMA in 1962 it had migraine as the main classification of headache and underneath the name migraine were listed different types of migraine such as common migraine, classical migraine, hemiplegic migraine, and at the bottom—cluster headache.

That is, cluster headache was originally listed as a type of migraine, but that was long ago and now the International Classification of Headache Disorder, first published in 1988, and now called ICHD III, classifies cluster headache separately from migraine and termed a Trigeminal Autonomic Cephalgia.

WHAT IS CLUSTER HEADACHE?

Here's the definition from the "Bible" of headache for the world, The International Classification of Headache Disorders-3. Cluster headache is:

A. At least 5 attacks fulfilling B-D below.

B. Severe unilateral orbital, supraorbital, and/or temporal pain lasting 15 to 180 min.

C. Attack is associated with at least one of the following signs on the side of pain:

1. Conjunctival injection
2. Lacrimation
3. Nasal congestion
4. Rhinorrhea
5. Forehead and facial sweating
6. Miosis
7. Ptosis
8. Eyelid edema

D. Frequency: from one every other day to eight per day

E. At least one of the following:

1. History, physical, and neurological examinations do not suggest disorders in groups 5-11 of IHS classification.
2. History and/or physical and/or neurological examinations do suggest other disorder, but it is ruled out by appropriate investigations.
3. Such disorder is present, but tension-type headache does not occur for the first time in close temporal relation to the disorder.

CLINICAL FEATURES

During the cluster headache in addition to pain the patient may experience symptoms on one side of the face around the eye, upper cheek, or temple. These symptoms may be:

- drooping of the upper eyelid (ptosis)
- smallness of one pupil (miosis)
- sweating above the eye
- redness of the eye (conjunctival injection)
- tearing of one eye (lacrimation)
- nasal congestion or drainage of clear fluid (rhinorrhea)

These "sinus" type symptoms many times bring the patient to the general doctor or ear nose throat surgeon with a self-made diagnosis of "sinus headache" with resultant treatment with repeat doses of various antibiotics or occasional sinus surgery.

RELATED QUESTIONS.

1.What is the pain of cluster headache like?

The pain begins quickly, without warning. It is excruciating in intensity and explosive in quality. Rarely the pain is pulsatile. Patients describe the headaches as "killer" headache[i] or "suicide headache." The pain may be "boring, stabbing, burning, like a knife, like a hot poker in the eye" and sometimes "pulsating, throbbing, squeezing, or aching." At the end of the attack the symptoms resolve in 1-2 minutes.

2.Where is the location of the pain from cluster headache?

The pain of cluster headache is located in one temple and behind or above one eye. Sometimes the face, neck, ear, or one side of the head may be involved. Cluster headache pain is persistently one sided in location. Migraine without aura headaches are unilateral 60-70 % of the time but cluster headaches are always one sided. Migraine may switch sides back and forth, the patient usually stating that one side is more prominent, but cluster headaches are strictly one sided and switches sides in 15% of patients usually for the duration of a bout. Very rarely the pain will switch sides during the cluster period.

3.What are the other symptoms found with cluster headache?

The patient may have characteristic autonomic symptoms during the attack. Lacrimation from the eye affected with pain is the most common associated symptom. The autonomic nervous system is a wired nervous system connecting the brain through the spinal cord and ganglia to a target organ. For instance, with tearing the autonomic nervous system connects to the lacrimal gland to produce tears in the eye. The autonomic nervous system fibers enter the eye wrapped around the carotid artery, and go to specific anatomical areas. These autonomic fibers innervate the pupil causing dilatation or constriction, the nasal turbinates to produce mucus, and a small muscle in the upper eyelid which helps hold the eyelid up. Autonomic fibers also innervate the sweat glands over the forehead and the blood vessels which course over the surface of the conjunctiva--the white part of the eye.

All of the so-called autonomic symptoms of cluster headache reflect altered, usually temporarily, dysfunction of the different fibers. Not every cluster headache patient has all the symptoms on the list, but commonly they may have three or four of the cardinal symptoms. Usually family members will comment about the upper eyelid drooping, a medical condition called ptosis. A small pupil on one side may be noted by a family member or the patient, but only if they are very observant. Redness of the conjunctiva, which is the white part of the eye, may be noted by the patient if they look at themselves closely in the mirror. Tearing, called lacrimation, or nasal dripping and congestion are usually pretty obvious. In my experience forehead sweating is not a prominent symptom and may not be noted by the patient.

Sometimes a patient with chronic cluster headache may develop an upper lid/pupillary syndrome related to damage to the tiny autonomic fibers in the carotid artery on that side called Horner's Syndrome. Patients with Horner's syndrome present with mild upper lid drooping so that the lid may fall down below the colored part of the eye. This is usually not bad enough to obscure vision and may just be a few millimeters of change. Also Horner's syndrome is associated with smallness of the pupil on one side, a condition called miosis. There may also be lack of sweating, called anhydrosis, over the up-

per forehead and so many a medical student memorizes the classical physical findings of Horner's Syndrome--ptosis, miosis, and anhydrosis.

Nausea, vomiting, and sensitivity to light and sound may occur with cluster headache, but these symptoms are not as prominent as they are in migraine without aura.

4.What are the onset and duration of attacks like?

Cluster headaches come without warning and reach a peak within 2-15 minutes. This is different from a typical migraine without aura attack which may take half an hour to several hours between onset and peak of headache pain. Cluster headaches are very severe, quick onset, one sided headaches which consist of pain around the eye, temple, or cheek. Cluster headaches may track the clock, coming at the same time every day. This periodicity is a key feature of cluster headache; the attacks of pain recur at the same hour each day for the duration of the cluster bout.

The attacks characteristically occur one to two hours after going to sleep in half of patients. An attack at this time corresponds with dreaming and REM stage sleep. Some patients have several attacks at night consistently interrupting sleep. Some patients get daytime attacks associated with napping or relaxation. Seventy-five percent of attacks occur between 9 p.m. and 10 a.m.

The duration of the attacks ranges from 15 to 180 minutes, with most cases lasting about 30 minutes to 2 hours with a mean of 45 minutes. The attacks may occur 1 to 8 times a day and the patient is pain free between attacks.

5.What does "cluster" mean in relation to these attacks?

The headaches come in time periods called "clusters" which usually last 6-12 weeks. The term "cluster" here means that the headaches cluster together in time, much like grapes cluster together on the vine.

Thus, the patient may state that he had 6 weeks of headaches in March and April of 2004, but then the headaches completely stopped. Following this there were no headaches in all of 2005, but they started again in March of 2006 and brought the patient to the doctor.

Although the usual cluster period is 1 ½ to 3 months, 10% of patients develop chronic cluster type headaches all year round and in these patients the "cluster" term is meaningless.

Also cluster patients may cycle between intermittent or the typical "cluster" pattern and chronic daily cluster headaches. Chronic cluster patients may evolve into the episodic form without treatment.

Although some cluster periods occur in the spring and fall, other researchers have found cluster cycles in February and June that seem to occur at the time of increase in daylight hours. Cluster attacks occur 7 to 10 days before the longest and shortest days in the year, suggesting that the pineal gland located in the center of the brain may be involved. The pineal gland responds to ambient light and helps set the sleep cycle.

6.What is the behavior of a patient like during an attack?

The patient usually gets up and paces around the room. Sometimes they may sit but they don't lie down in bed in a quiet room with the lights out like a typical migraine patient would do and they don't miss work like a migraine patient would.

Blau in 1993[ii] wrote an article in The Lancet on the "Behavior during a cluster Headache." Blau stated:

Walking with the trunk slightly bent forwards and clutching the head, or sitting and rocking backwards and forwards with the hands pressed on or near the painful site, was the most common behavior during attacks.

Self-trauma, a common feature, included pressing a finger, thumb, or fist into the affected eye or adjacent temple, hitting the forehead against a hard object (wall, floor, radiator, or mantelpiece), or rubbing or pressing the forehead on the affected side on the carpet or chair; others repeatedly hit or painfully scratched the head distant from the painful site; one rubbed his thighs until they became red and sore. Clenching fists so that the finger nails dug into the palms, applying intense heat ("a boiling cup of tea or a hot water bottle"), or ice-cold objects to the forehead were also described. In two patients with lower-half cluster headache (pain radiating to the upper jaw instead of upwards over the head), one inserted and twisted a steel knife blade between the painful upper teeth, while another pushed a finger nail as hard as he could into a tooth socket in the painful region. Three pushed a cotton wool tip up the affected nostril while another blew his nose very hard, each to provoke the rhinorrhoea that heralded the end of their attacks.

Dr. Karl Ekbom[iii]

Ekbom[iv] noted the inability of cluster headache patients to remain still during attacks, in contrast with migraine patients who want to lie completely still.

7.What aggravates the cluster attacks?

Another interesting feature is that cluster headache may be aggravated by alcohol consumption only during the cluster period in about half the patients. If a migraine patient reacts to a certain alcoholic drink, the migraine may come on anytime the patient imbibes that type of alcohol. The cluster headache patient may say that a beer or glass of red wine will immediately set off a headache during the 6-12 weeks when the headaches come, but alcohol has no effect on inducing headache between cluster attacks.

The vasodilator, nitroglycerin, known to treat vasospastic angina pectoris characteristic of coronary artery disease, given as 1 mg sublingually triggers an attack during a bout. Histamine may also provoke an attack.

8.What are patients with cluster headache like?

The patients often have a driven, type A workaholic nature. They tend to be ambitious, efficient, conscientious, striving, compulsive, self-controlled, self-sufficient, reserved, and tense. They also tend to smoke cigarettes and drink alcohol more than the usual person.

I recall a patient I saw years ago who had cluster headache and the typical driven lifestyle some of these patients have. In his small-town he was the sheriff, voluntary fireman, and emergency ambulance attendant. He did these jobs on the side while running his family business during the day. He carried four beepers.

At the June 1985 Second International Headache Congress in Copenhagen Dr. John R. Graham[v] of the Headache Research Foundation, Jamaica Plain, Massachusetts stated that "Most patients with cluster headaches are men who are considered 'Macho.'" Dr. Graham thought that "the few women who got cluster headaches tended to have square, boyish faces, and to be masculine in appearance."

At the same meeting Dr. Lee Kudrow,[vi] of the California Medical Clinic for Headache, Encino reported that men with cluster headaches were as much as 3 inches taller than the average and had characteristic facial features with deep asymmetrical facial creases.

Continued on page 22

There is also a relationship between cluster headache and obstructive sleep apnea.[vii]

9.What is the nosology, (the branch of medical science dealing with the classification of disease) of cluster headache?

The title itself, cluster headache, causes confusion in the lay and in some doctors' minds. Several times a month I'll talk with a headache patient who will tell me that their doctor said they had "cluster headache," because the patient had several headaches in a row. Usually the patient has migraine without aura that is partially treated with acute therapy medication and the patient has one big long headache with peaks and valleys. Many of these patients have a diagnosis of medication overuse headache and have central sensitization.

There was a lot of confusion in the literature when the syndrome of what is now universally called cluster headache was first recognized. At the start of my career in the late sixties I was taught to call this type of headache "vasodilating" headache which I did for a few years until the "cluster" term rose to prominence and then stuck.

Other names offered for cluster headache have been migrainous neuralgia, histamine headache, histamine cephalalgia, Horton's headache, Ciliary neuralgia, Sluder's sphenopalatine neuralgia, geniculate neuralgia, Raeder's paratrigeminal neuralgia, erythroprosopalgia, Raeder's syndrome, vidian neuralgia, red migraine (because the white part of the eye turns red), periodic migrainous neuralgia, ciliary (migrainous) neuralgia, greater superficial petrosal neuralgia, and anterior migraine.

Cluster headache is now firmly established as a distinctive syndrome. Finally it was understood that all of these conditions had similar symptoms and that different doctors in different parts of the world had been describing the same thing.

10.What is the epidemiology of cluster headache?

Cluster headache occurs in approximately 69 cases per 100,000 people, and is far less common than migraine. Men are affected more than women at a rate of 6:1. It usually occurs between the ages of 20 to 50 years with a mean of 30 years; however, it may begin as early as the first decade and as late as the eighth decade. Attacks in women with cluster headache usually do not correlate with their menses, generally stop during pregnancy, but like migraine may be started by the use of oral contraceptives. Women may have both cluster headache and migraine but they are commonly misdiagnosed only with migraine.

11.Does cluster headache occur in women?

Rozen, et al,[viii] writing in the Journal of Neurology, Neurosurgery, and Psychiatry in 2001 studied the clinical features of cluster headache in women and found that their experience was similar to men. Women develop cluster headache earlier than men with the mean age of onset at 29 years in women as opposed to 31 years in men. Women had 2 peaks of onset in the 2nd and 5th decade, whereas men peaked at 31 years. Women had more "migrainous symptoms" with cluster headache, especially vomiting, but both men and women had frequent sensitivity to light and sound. Rozen, et al,[ix] pointed out that the symptoms of photophobia and phonophobia are not included in ICDH II cluster headache criteria but he thought that the criteria needed revision to include them.

Cluster headaches used to occur mainly in men and a ratio of men/women of 6/1 was commonly quoted in the past, but recent articles suggest that women are getting the syndrome more often, perhaps related to the stress of women leaving the home and entering the workplace. Bahra, et al,[x] wrote in Neurology in 2002 on "Cluster headache. A prospective clinical study with diagnostic implications." They stated that "The overall male-to-female ratio in this sample was 2.5:1, and this has decreased with time." Also Manzoni[xi] wrote an article in 1997 in Headache entitled "Male Preponderance of Cluster Headache is Progressively Decreasing Over the Years."

12.When does cluster headache start?

The typical age of onset is the third decade which would be 20 to 30 years old but the range extends from 20 to about 60 years old. Many persons with cluster headache have family members with migraine.

13.What does the literature say about cluster headache?

The history of the various terms used to describe this painful disorder has a long serpentine story weaving back into the eighteenth century. Most authors give early credit to the description made by von Mollendorff,[xii] who in 1867 described "red migraine with hemicrania, homolateral redness of face, injection of the eye, lacrimation, and dilatation of the temporal arteries." However, an earlier report was made by Gerhard van Swieten[xiii] who gave a full description of episodic cluster headache which fulfills IHS criteria in 1745 in his textbook of clinical medicine. Van Swieten was the founder of the then leading medical center, the Vienna school. His article, lost because it was originally written in Latin, was found again and translated in 1992.

Wilfred Harris (1869-1960) [xiv]

In 1926 Wilfred Harris[xv] described a special recurrent headache which he called "Periodic Migrainous Neuralgia." In

1936[xvi] in the British Medical Journal Harris wrote about the subject again using the title of "Ciliary (Migrainous) Neuralgia." Harris was the first to describe successful treatment of the acute attack of cluster headache with ergotamine.[xvii] In his 1936 article Harris offered his "Definition of Migrainous Neuralgia":

I have employed the term "migrainous neuralgia" to describe cases of recurrent neuralgia affecting the temple or the side of the forehead and often both jaws, sometimes extending to the back of the head, usually strictly unilateral. The pain in these cases is often most intense and excruciating, and may start suddenly or gradually and subside in the same way, the duration of the pain varying from ten minutes to half an hour, or often for five or six hours and occasionally for twenty-four hours for periods of six to eight weeks yearly. Nausea occasionally accompanies the pain, suggesting its association with migraine, but vomiting is rare, and visual spectra and transient hemianopia are never met with as in the usual form of migraine.

Case II from Harris' 1936 article on Ciliary (Migrainous) Neuralgia follows:

In one case, indeed, a man of 40 suffered almost continually for three weeks, having had only eight hours; sleep during that period. His first attack began when he was aged 37, and the longest interval between attacks was two months, the severe pain lasting usually one or two weeks, being continuous and limited strictly to the left eyeball.

Harris stated:

The pain is described by various sufferers as "intensely severe"; "very excruciating"; "the eye feels as though being hammered or rolled on the ground"; "the eye feels as if it were being pulled out, or turned inside out"; "like boiling water behind the eye."

Bayard T. Horton (1895-1980) [xviii]

Horton, et al,[xix] spoke about a new syndrome which they originally named "erythromelalgia of the head" in 1939 but changed to "histamine cephalalgia" in 1941.[xx] Horton[xxi] at the Mayo Clinic called the syndrome "histamine headache" in 1939. One of Horton's cases from his 1939 article follows:

Vasodilating pain in the left eye, associated with a left hemicrania, and precipitated by the drinking of beer--A man, aged 58 years, gave a history of recurring bouts of pain in the left eye of twelve months' duration. The attacks occurred either during the day or night and often awakened him from a sound sleep.

The onset of the pain was gradual and was localized behind the left eye. It was of a constant, sharp character, but no throbbing sensation was present. When the pain lasted more than one and a half hours, it extended to the left temporal and occipital regions and into the neck. It decreased in the orbital region as it increased in the occipital region. This pain often persisted for four or five hours, without associated nausea or vomiting. The drinking of alcoholic beverages, particularly beer, invariably precipitated an attack of pain in the left eye after an interval of thirty to fifty minutes. The pain was reproduced on three different occasions by having the patient drink a bottle of beer. Compression of the left common carotid artery gave momentary relief.

Gardner, et al,[xxii] introduced "greater superficial petrosal neuralgia" in 1947 and suggested treatment by resecting the nerve. "Cluster headache" was used by Kunkle, et al,[xxiii] in 1952 and then by Friedman and Mikropoulos[xxiv] in 1958.

In 1956, Sir Charles Symonds[xxv] writing in Brain gave a more complete account of the syndrome of cluster headache in an article entitled "A Particular Variety of Headache" which helped to educate the general medical audience and the public about this little known malady. Symonds stated about the syndrome:

Its essential features are the occurrence of paroxysms of headache, that is to say, pain of sudden onset and transitory duration, which occur in bouts lasting as a rule for several weeks with long intervals of perfect freedom. In the paroxysm the pain is felt mainly in the supra-orbital region or in and behind the eye, though it may spread beyond this region. It is, however, strictly unilateral. It is of agonizing severity, but very rarely lasts longer than two hours and often less. During a bout there is usually at least one paroxysm in each 24 hours; there may be more. In the intervals between paroxysms there is complete relief. The bout having ended, there is no further complaint of headache until the occurrence of the next bout after an interval of freedom, which is rarely less than 6 months and may be several years. No local cause for the pain is to be discovered in the shape of disease of the eyes, nose, nasal sinuses, ears, scalp or skull, or the sensory nerves supplying the region where the pain is felt.

A report of Symonds' case 1 follows:

Male, aged 39 when first seen in 1948. At the age of 35 began to have attacks of pain behind the left eye described as like pain in a tooth exposed to cold, reaching peak intensity in 15 minutes, remaining thus for an hour or an hour and a half, and rapidly disappearing, but sometimes followed by a dull ache for an hour or two. At the height of the attacks the eye would water and become bloodshot and the left side of the nose would feel blocked. The attack would usually begin between 2 a.m. and 3 a.m. and would be repeated for two or three nights in succession. After an interval of six or eight weeks the experience would be repeated.

When seen again in November 1955, he reported that the nature of the attacks had remained unaltered, but that the series or bout had gradually become longer, lasting up to a fortnight, and the intervals between bouts had also lengthened to six months. Then in the summer 1952 he had a bout lasting four weeks followed by complete freedom for eighteen months. There was then a bout lasting two weeks, again followed by freedom for eighteen months, when he began a bout which had lasted for five weeks when he was seen. In this the paroxysms had occurred at irregular times, mainly during the night, but occasionally during the day. On two occasions there had been three paroxysms in the twenty-four hours. But on several occasions he had gone twenty-four hours without a paroxysm.

14. What is the current understanding of cluster headache?

Cluster headache is now considered to be one of the trigeminal autonomic cephalalgias, a group of primary headaches which includes paroxysmal hemicrania and Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing (SUNCT). The area of the brain involved with cluster headache is the posterior hypothalamic gray matter. In contradistinction the area of the brain involved with migraine is located in the brainstem.

Goadsby and Lipton[xxvi] stated in a review of this subject in Brain in 1999:

The short-lasting primary headache syndromes may be conveniently divided into those exhibiting marked autonomic activation and those without autonomic

Continued on page 23

activation. The former group comprises chronic and episodic paroxysmal hemicrania, short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT syndrome) and cluster headache. These headache syndromes are compared with other short-lasting headache disorders, such as hypnic headache, and persistent headache with milder autonomic features such as hemicrania continua. Cluster headache is included with the shorter-lasting headaches to attempt a nosological analysis of these syndromes. The paroxysmal hemicranias are characterized by frequent short-lasting attacks of unilateral pain usually in the orbital, supraorbital or temporal region that typically last minutes. The attack frequency usually ranges from 5 to 40 attacks per day. The pain is severe and associated with autonomic symptoms such as conjunctival injection, lacrimation, nasal congestion, rhinorrhoea, ptosis, or eyelid oedema. Almost all reported cases respond to treatment with Indomethacin, but respond poorly to other treatments including other non-steroidal anti- inflammatory drugs. A recent case study demonstrated the release of both trigeminal and parasympathetic neuropeptides during a bout of pain in the same pattern previously described in cluster headache.

15.What is the ICHD 3 classification of cluster headache?

Cluster headache and other trigeminal autonomic cephalalgias

3.1 Cluster headache

3.1.1 Episodic cluster headache

3.1.2 Chronic cluster headache

3.2 Paroxysmal hemicrania

3.2.1 Episodic paroxysmal hemicrania

3.2.2 Chronic paroxysmal hemicrania (CPH)

3.3 Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT)

3.4 Probable trigeminal autonomic cephalalgia

3.4.1 Probable cluster headache

3.4.2 Probable paroxysmal hemicrania

3.4.3 Probable SUNCT

16.Peter Goadsby[xxviii] statement writing in Lancet Neurology in 2002 on "Pathophysiology of cluster headache: a trigeminal autonomic cephalgia," stated:

Cluster headache is a form of primary neurovascular headache with the following features: severe unilateral, commonly retro-orbital, pain accompanied by restlessness or agitation, and cranial (parasympathetic) autonomic symptoms, such as lacrimation or conjunctival injection. It occurs in attacks typically of less than 3 h in length and in bouts (clusters) of a few months during which the patient has one or two attacks per day. The individual attack involves activation of the trigeminal-autonomic reflex; thus, such headaches can be broadly classified with the other trigeminal-autonomic cephalgias, such as paroxysmal hemicrania and the syndrome of short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing. Observations of circadian biological changes and neuroendocrine disturbances have suggested a pivotal role for the hypothalamus in cluster headache. Functional neuroimaging with PET and anatomical imaging with voxel-based morphometry have identified the posterior hypothalamic grey matter as the key area for the basic defect in cluster headache.

17.What is Cluster-tic syndrome?

There also are patients who have both cluster headache and trigeminal neuralgia (tic douloureux). This may be called the "cluster-tic syndrome." The patient should receive both diagnoses and be treated for both conditions.[xxix]

18.How medicine has changed?

Horton[xxx], at the Mayo Clinic and well experienced with cluster headache said: "Error in diagnosis is usually due to the fact that the physician has not had the opportunity to observe the patient in the course of a spontaneous or induced attack."

What Horton described is usually no longer possible since the doctor and the patient now interface at the clinic in the doctor's office usually between attacks and the patient describes a history of something that had happened in the past, rather than the doctor seeing the patient at home in his native environment and observing an attack.

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Kennedy Disease

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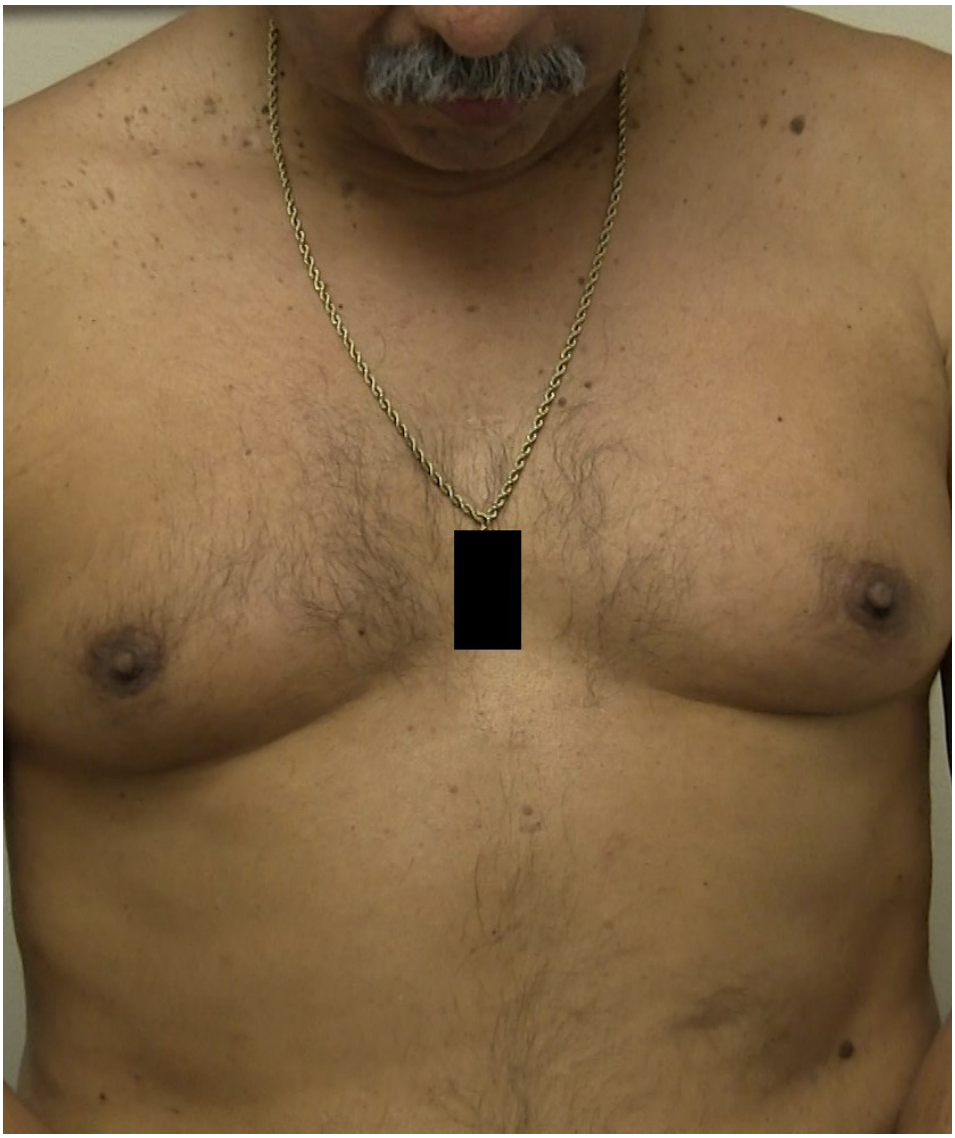
DANCING MUSTACHES SIGN IN KENNEDY DISEASE

A 66-year-old male presented with weakness and muscle wasting in the lower and upper extremities which started 2-3 years earlier. Recently, he lost 25 pounds and he suffered muscle twitching and cramping. The patient denied any sensory loss, coordination deficit, visual or speech symptoms. Upon Physical examination, the patient showed fasciculation in the face (Dancing Mustaches sign), extremities and chest along with gynecomastia (see picture) and wasting of the hand's muscles. Deep tendon reflexes were diffusely absent. Electromyography revealed evidence of widespread chronic motor neuron disease. His serum level of Creatinine Kinase was elevated. There was no family history of muscle diseases. Genetic testing showed 40 CAG repeats in the androgen receptor (AR) gene which is characteristic of Spinal and Bulbar Muscular Atrophy (Kennedy Disease). The patient was advised on the nature of the X-linked disease.



Kennedy disease (spinobulbar muscular atrophy) is an X linked neurodegenerative motor neuron disease and is caused by mutation of the androgen receptor gene.

Affected males display manifestations of the disease most commonly in the middle adult life. Symptoms and signs reflect spinal and bulbar lower motor neuron dysfunction and include muscle cramps and atrophy, weakness, dysarthria, dysphagia and areflexia. Androgen receptors insensitivity leads to gynecomastia, testicular atrophy, and erectile dysfunction. The genetic defect is expansion of the CAG repeat in the first exon of the androgen receptor gene leading to a toxic gain of function. Severity of the disease correlates with the degree of expansion. CPK elevation is more typical than the other motor neuron diseases such as ALS and SMA due to reinnervation. Impaired vibratory sensation in the feet is common and may be due to involvement of the sensory neurons. Treatment is conservative. The disease shortens life expectancy by 10-15 years.

Dancing mustache video: https://www.youtube.com/watch?v=WF-pQF-eArzU&feature=youtu.be

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