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A Closer Look at AR-IMPACT

Accessible, Relevant CE for Prescribers Navigating Pain Management During the Opioid Epidemic

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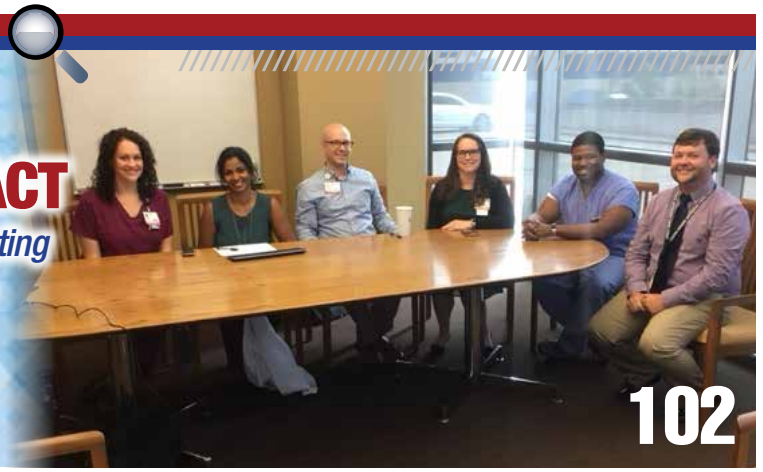
by CASEY L. PENN

ON THE COVER

A Closer Look at AR-IMPACT

Accessible, Relevant CE for Prescribers Navigating Pain Management During the Opioid Epidemic

A weekly, interactive continuing education seminar, AR-IMPACT is designed to help the state's prescribers navigate pain management during an opioid epidemic. Find out more about AR-IMPACT and its leadership team on page 102.



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Winner of the ASAE Excellence in Communications Award

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COMMENTARY

The Power of Vulnerability

Issam Makhoul, MD

The first encounter with a patient brings two strangers face to face to engage in a special relationship. It's a balance of forces where either (1) the strongest dominates the scene or (2) a partnership develops based on mutual understanding, respect, and common goals. In the first type of relationship, the patient brings in her problems, expectations, and prejudices while the physician brings in her knowledge and authority, ever bolstered by the social power of the physician's white coat. After the usual icebreakers, the balance starts shifting toward the physician who sits in the inquisition seat, asking questions, digging deeper and deeper into her personal story looking for the most intimate details. The balance shifts even further toward the physician during the physical exam that completes the undressing of the patient literally and figuratively. Standing naked in front of a stranger places the patient in a position of considerable vulnerability. Furthermore, in many medical encounters, this vulnerability gets worse by the way health care providers focus on the case and ignore the person and her perception of reality. For the patient, the symptoms and her personal perception of them are at the center of the visit, and the disease pattern does not exist. For the physician, the disease pattern is the focal point, and the personal details are trivial. In this scenario, the physician's knowledge, authority, and power ultimately tip the balance away from the patient.

How can we reconcile these two ways of looking at reality, and whose responsibility it is to steer the encounter toward the second type of relationship? And, since partnership implies equality between partners, can the physician truly be equal to the patient?

Moving toward a partnership is the physician's responsibility, and it can be accomplished by engaging on two axes at the same time: recognizing the disease pattern and its best treatments and discovering the unique story of the patient and always integrating the patient's perception into the story. Sharing elements of the physician's personal life may be appropriate in some circumstances. I have occasionally done it, and most of the time I felt this was not the answer. The patients do not necessarily want to hear about us. Listening to their story and giving them control of the time with us is what they want. Showing vulnerability by giving them access to our hearts and touching them with our hands during the physical exam shows them that we care. In their struggle to restore their health, our patients need reassurance that we will do everything we can to help them. They need to know that there is hope for regaining control of their lives and redefining the meaning of living now and here.

> *"In the beginning is the hearing"*
> ~ Nelle Morton

Giving patients access to our heart and our time creates a balanced relationship. One of my colleagues once told me that she gave her patients her personal phone number. My first reaction was to be fearful that this would be a major intrusion into my personal life if I were to do it. She said, "Try it, they do not abuse it." And I did. Indeed, I found out that 99% of the time, they use it with respect and consideration. On the other hand, doing so strengthened my relationship with them significantly and made them more compliant with their treatment plans. Occasionally, it was a life-saving means as I could direct the patients to the emergency room instead of them wondering in silence about what to do. It is a form of exchanging vulnerability; surprisingly, being *exposed* to each other, being *vulnerable,* helps each party feel stronger and builds trust.

Interestingly, the restorative effects of this type of relationship go beyond the positive impact on the patient's life. Indeed, the healing effects are reciprocal and profound for the physician. As Emily Style says, "When we hear another out, glancing through the window of their humanity, we can see our own image reflected in the glass of their window." This type of relationship gives our life a meaning and restores to it a sense of purpose. At a time when our medical community is assailed by numerous unbearable pressures that are causing burnout and sometimes physician suicide, it is time to jump with our patients into the boat of our shared humanity. This is a goal and a means for salvation for all of us. AMS

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by CASEY L. PENN

A Closer Look at AR-IMPACT

Accessible, Relevant CE for Prescribers Navigating Pain Management During the Opioid Epidemic

Last month in *The Journal*, we touched on a new continuing education seminar, AR-IMPACT (Improving Multi-Disciplinary Pain Care Treatment). This month, we bring you a closer look at this free resource that has the potential to add more to your prescribed treatment regimen than a few required hours.

"Even as a facilitator and panel member, I can say that my practice has been dramatically improved," said AR-IMPACT Panelist Johnathan Goree, MD. An anesthesiologist and director of Interventional Pain Management Services at UAMS, Dr. Goree treats chronic pain conditions using opiate-sparing, minimally invasive procedures and conducts associated research. "I've developed relationships with skilled providers that I can consult when I encounter problems, and I have learned things that have transformed my practice. I hope physicians who [participate in] our calls have the same experience."

AR-IMPACT was a creation of G. Richard Smith, M.D., medical director of the Drug and Misuse and Injury Prevention Branch and a professor in the departments of Psychiatry, Medicine and Public Health at UAMS**.** In a video explaining the concept, Smith said, "We are all concerned about the opioid epidemic, especially here in Arkansas, where we have the second highest rate of opioid-prescribing in the nation.

"Much of the opioid problem extends beyond health care. Those of us who are health care providers need to do our part to reduce unnecessary reliance on opioid in the care of patients with chronic pain. This weekly, free CME conference is designed to help prescribers improve the treatment of chronic pain."

Structure & Topics

AR-IMPACT is delivered via tele-video conference at noon on Wednesdays. Seminars are streamed real-time from arimpact.uams.edu. However, participants who prefer may also participate on-site in Conference Room 136 of the UAMS Psychiatric Research Institute. (Parking coverage is available for individuals participating onsite.)

Weekly seminars are free for the taking – for now. "We have funding through March 2019 currently," said AR-IMPACT Director Corey Hayes**,** Pharm.D, MPH, who has applied for and hopes to receive funding to cover an additional year. The program is presented by UAMS and funded by Arkansas Blue Cross and Blue Shield and the Office of the State Drug Director, and in partnership with the Arkansas Medical Society, the Arkansas Academy of Family Medicine, the Arkansas Department of Health, and the Arkansas State Medical Board.

Hayes is an assistant professor of health services research at UAMS's Psychiatric Research Institute and a research health scientist for Central Arkansas Veterans Healthcare System. He told *The Journal* that AR-IMPACT was designed to help prescribers manage their patients with chronic pain and related anomalies while minimizing the use of and/or tapering opioids where possible.

Each seminar begins with a brief presentation by AR-IMPACT panelists and ends with discussion and instruction related to real patient cases. Guest speakers present periodically as well. "We were chosen based on our ability to provide expertise in areas centered around opioid use," said Panelist Shona Ray-Griffith, MD, a perinatal psychiatrist and assistant professor in UAMS's Departments of Psychiatry and Obstetrics & Gynecology. "In my practice, I understand and treat mental illness, of course, but also addiction – specifically opiate use disorder. My role is to speak to these issues, which are fundamental to the treatment of chronic pain."

Panelists hold expertise in addiction management, psychology, physical therapy, clinical pharmacy, pain management, and general medicine/geriatrics/palliative care. In addition to Drs. Ray-Griffith and Goree, they include Michael Cucciare, Ph.D.; Masil George, MD, Leah Tobey, PT, DPT; and Teresa Hudson, Pharm.D., Ph.D**.**

Topics vary, but always focus on some aspect of chronic pain. Hayes, a pharmacist, has presented a summary of the 2016 CDC guidelines on prescribing for chronic pain and discussed how to interpret the new Prescriber Feedback Reports issued by the Arkansas Department of Health. Dr. Ray-Griffith has presented about addiction and the use of buprenorphine for chronic pain, and she recently presented a discussion of patient-centered research comparing opioids to non-opioid therapies for chronic pain.**

Those are but a few examples. Upcoming conference schedules and presenters are listed on the website – a good place for physicians to start.

"They can pick and choose what is most helpful at a given time or what simply piques their interest," said Dr. Ray-Griffith, who has found her own interest piqued by topics covered; these have included **Screening for Depression and Anxiety in Patients with Pain**, **The Evidence for Medical Marijuana and the Impact on Opioid Use**, **Opioid Tapering**, and more."If participants don't find a topic they deem helpful, they're encouraged to bring their own cases to the panel for discussion. The presentation portion of each seminar is meant to cover the first half of the hour. The second half is meant for prescribers to come to us with a case they want to talk about. For example, both Dr. Ray-Griffith and Dr. Goree have presented patient cases from their own clinics in the past.

"Physicians can verbally speak to us during the session about a case they'd like to discuss, or they can write that in real time using the chat window. Either way, they've let us know to keep the presentation short to leave plenty of time for

them. They can even email us ahead of time at ar-impact@uams.edu with a case to discuss – especially if they have a specific date they want to bring the case."

Formatted for Meaningful Participation

"AR-IMPACT is different from typical online CME," said Hayes of a format that encourages discussion and problem solving associated with physicians' ongoing cases.

Interactivity and *convenience* are two main keys to the program's value, shared Dr. Ray-Griffith. "It's interactive, highly relevant to you and the patients you're trying to treat, and you can participate, if you like, from your office during lunch or between patient loads," she said. "We know physicians are busy. They can sit and eat while listening, and soon, they will be able to go online at a later time to watch archived seminars."

"The majority of physicians have never had a lecture on improving pain management," said Dr. Smith. "If you're worried about your opioid prescribing, AR-IMPACT is a way to help yourself. If you wanted to, you could get all your continuing education for an entire year from it in 20 sessions."

Participation is growing, and currently stands now at between 20-30 attendees each week. "We have issued 280 CE credits since starting in May," Hayes added. "Currently, they are not available, but we are in the process of working with UAMS Learn on Demand to make past conferences available online for viewing and free CE credit."

Filling a Gap

AR-IMPACT is about more than CE credits, as Smith and AR-IMPACT team members have indicated. It's about giving physicians needed resources to deal with this evolving problem. Hayes shared with us the feedback of one participant (anonymous), who praised the panel-to-participant discussions and said, "I applaud your acknowledgement that we in primary care have a difficult task in managing these patients."

Dr. Ray-Griffith identified with the participant. "I'm a psychiatrist. I've seen addiction and treated people with addiction, but when this became an issue nationally, even I was amazed at the severity of the problem. I think everyone at some point has been surprised. And the problem in Arkansas is evolving. For example, if you would have asked me two years ago about heroin, I would have said 'We don't have heroin in the state of Arkansas,' and in fact, in training, I never saw a patient who had used heroin. Now, almost every patient I see for opioid use disorder is primarily using heroin or has used heroin.

"Health care providers are trying their best for patients. Opioids were initially thought as helpful; however, we are now realizing the dangers of chronic opioids."

One problem, said Dr. Ray-Griffith, has been a lack of evidence to support *other* modalities. "That's what we're trying to get out there with programs like AR-IMPACT," she stressed, demonstrating the change in approach. "… Here's what the evidence says. Here's what you need to know about *other* ways to treat chronic pain. AR-IMPACT is here to help you taper opioids, find alternatives approaches, recognize an opioid use disorder, explore who is the right patient to be on chronic opiates as well as address any co-occurring depression and anxiety."

As we have and will continue to report, physicians and other stakeholders (researchers, legislators, others) are hard at work to confront this

> Continued on page 104.

epidemic in Arkansas. AR-IMPACT is one example of a program that is available to help you learn more about navigating pain management during the opioid epidemic. Visit ARIMPACT.uams.edu for upcoming topics, AR-IMPACT team bios, and a hefty resource section. Follow AR-IMPACT on Twitter (@ArkansasImpact) or Facebook (search *Arkansas Impact*) for conference reminders and other useful tips.

**The author credits AR-IMPACT panelist Johnathan Goree, MD, for this most-fitting article title.*

***Effect of Opioid vs Nonopioid Medications on Pain-Related Function in Patients with Chronic Back Pain or Hip or Knee Osteoarthritis Pain, The SPACE Randomized Clinical Trial. JAMA. 2018;319(9):872–882. doi:10.1001/jama.2018.0899* AMS

AR-IMPACT Team

Source: arimpact.uams.edu

Michael Cucciare, Ph.D., is an associate professor in the Department of Psychiatry at UAMS. He is trained as a clinical psychologist and treats perinatal women with opioid use disorder in the UAMS Women's Mental Health Program. He has expertise in evidence-based mental health interventions for treating substance use disorders including relapse prevention, cognitive-behavioral therapy, and motivational interviewing. He is also an addiction health services researcher with over 10 years of federal funding.

Board certified in anesthesiology and pain medicine, **Johnathan Goree, MD**, is a proud alumnus of Catholic High School in Little Rock, Ark. He received his bachelor of arts in Biology from Washington University in St. Louis. He then moved to New York City where he completed both his medical degree and residency in anesthesiology at the Weill College of Medicine at Cornell University. Following his time in Manhattan, he completed a fellowship in interventional pain management at Emory University Hospital in Atlanta, Ga. In 2014, Goree returned home to Little Rock to join the faculty at UAMS where he serves as the director of Interventional Pain Management Services and an assistant professor in the Department of Anesthesiology. He primarily focuses on the treatment of chronic pain conditions using opiate sparing, minimally invasive procedures. His specific research interests include complex regional pain syndrome and neuromodulation for novel indications.

Corey Hayes, Pharm.D., MPH, is a post-doctoral fellow in the NIDA T32 Translational Training in Addiction program in the Department of Psychiatry at UAMS. He is trained as a pharmacist and before entering the fellowship, he spent three years working as a clinical pharmacist at Baptist Health Medical Center in Little Rock where some of his duties included acute care pain management and rounding with the psychiatric care team. Within his fellowship, he has been researching opioid use and abuse at the population level, including state level analyses.

Teresa Hudson, Pharm.D., Ph.D., was trained as a pharmacist with an emphasis in clinical use of medicines, quality of medication management and medication adherence. Hudson's research has focused on understanding the epidemiology of medication use and identifying strategies to improve the safe and effective use of medications for treatment of mental health disorders and understanding the physical health implications of medications to treat these disorders. More recently, Hudson has begun research in understanding the risks of opioid use among individuals who use these medications chronically and is participating in research to understand how pharmacists and physicians manage the risks associated with opioid medications.

Shona Ray-Griffith, MD, is an assistant professor in the Departments of Psychiatry (primary appointment) and Obstetrics & Gynecology (secondary appointment) at UAMS. She is a board-certified psychiatrist with clinical expertise in the management of a broad variety of neuropsychiatric illnesses. Within the Women's Mental Health Program, she focuses on the treatment of mental illness, substance use disorders, and chronic pain throughout pregnancy and the postpartum period. Her clinical research interests include the use of non-pharmacological treatments (e.g., electroconvulsive therapy, transcranial magnetic stimulation, exercise) as well as the course, outcomes, and treatment of chronic pain disorders during the perinatal period.

Leah Tobey, PT, DPT, graduated with her bachelor of arts from Ouachita Baptist University, received her doctorate in physical therapy from the University of Central Arkansas and is currently pursuing her master's in business administration at the University of Arkansas Little Rock. Tobey joined the UAMS physical therapy department in 2013. She is active in the evaluation and treatment of patients with orthopedic dysfunctions in addition to pelvic health rehabilitation.

Masil George, MD, is a family physician with fellowship training in geriatrics as well as hospice and palliative care. She has an interest in pain management in the elderly, and provides consultative service for palliative care in the geriatric outpatient clinic at UAMS. She also serves as the medical director for Baptist Hospice. Her goal is to get physicians in the community to refer patients to AR-IMPACT for recommendations on pain management options and assist them by providing medication advice but also potentially telemedicine pharmacy and behavioral medicine support.

by CASEY L. PENN

ASMB Regulation 2.4

Be Aware – Not Afraid – of New Rules Clarifying Excessive

Some AMS members are tired of hearing about Regulation 2.4, particularly the misconceptions surrounding it. Others have yet to hear a word about it. From either position, or anywhere in between, the fact is that Arkansas State Medical Board's recently adopted changes contain information that affects the physicians of Arkansas. The changes are relatively recent, so even at the risk of repeating ourselves, AMS is committed to sharing the latest developments.

Kevin O'Dwyer

During its April 2018 meeting, the ASMB adopted changes to Regulation 2, which states and governs the standard of care expected of physicians in Arkansas, and specifically, amendments made to section 2.4, which directs the prescribing of scheduled medications. Post-changes, the rule essentially accomplishes two things: it defines once and for all what is "excessive" when prescribing narcotics, and it establishes some stipulations for prescribers to follow.

In a June 2018 commentary and again during a Board of Trustees meeting in May, AMS Executive Director David Wroten touched on apparent confusion related to "the Rule."

"There's a lot of misinformation out there about this issue," Wroten explained, having witnessed the April ASMB meeting. "No *physicians* testified against the regulations, but a room full of *patients* testified against it. Most were catastrophic cases … These people were scared to death that they weren't going to be able to get their pain medications that they had been on for all this time … What they testified – was 'my physicians said with the medical board regulation, I can no longer write opioid prescriptions.'"

Wroten went on to clarify that Regulation 2.4 does ***not*** prohibit physicians from prescribing pain medications. "The rule discourages writing over 90, but it doesn't prohibit it," he said. "For those writing more than 50 MME per day for chronic pain, this rule establishes a list of things that must be documented in the medical record."

So then, why the confusion?

ASMB Attorney Kevin O'Dwyer believes physicians are simply misinterpreting the rule. "It's true that Regulation 2.4 is a detailed set of rules," said O'Dwyer, while also describing the rule as *unambiguous* and *hard to misinterpret*.

"Some physicians [and patients] may be reading things into it that just aren't there – like hard limits. It clearly does not set limits.* However, if you're going to go over 50 morphine equivalents, you must demonstrate several things that are outlined in 2.4. It sets markers, but the Board has always said that you must justify why you're prescribing. Historically, over-prescribing was prescribing ***one*** pill without justification. I think a lot of doctors are using 2.4 as reason to not prescribe or to explain to patients why they're not going to prescribe. From what I've heard from doctors, it's not only 2.4. It's the DEA, it's fear of federal prosecution, it's the PDMP, it's somebody watching your every prescription. These things cause more fear than 2.4, but 2.4 is new.

"*Patients* have called me and said their lawyer says this, or their doctor says this … No *lawyer* has called me. No *doctor* has called me. I don't know what the confusion is. It just says what it says."

With that in mind, here's a little bit of the rule itself:

Regulation 2.4 as Effective August 8, 2018

(Source: armedicalboard.org)

The prescribing of excessive amounts of controlled substances to a patient including the writing of an excessive number of prescriptions for an addicting or potentially harmful drug to a patient. "Excessive" is defined as the writing of any prescription in any amount without a detailed medical justification for the prescription in the patient record.

A. Chronic Pain: If there is documented medical justification, "excessive" is defined pursuant to the Centers for Disease Control (CDC) guidelines for prescribing opioids for chronic

> Continued on page 106.

Post-changes, the rule essentially accomplishes two things: it defines once and for all what is "excessive" when prescribing narcotics, and it establishes some stipulations for prescribers to follow.

pain, as prescribing opioids at a level that exceeds ≥ 50 Morphine Milligram Equivalents (MME) per day, unless the physician/physician assistant documents each of the following:

a. Objective findings, which include, but are not limited to, imaging studies, lab testing and results, nerve conduction testing, biopsy, and any other test that would establish pain generating pathology

b. Specific reasons for the need to prescribe ≥ 50 MED per day

c. Documented alternative treatment plans as well as alternative therapies trialed and failed prior to considering chronic-opioid therapy

d. Documented risk factor assessment detailing that the patient was informed of the risk and the addictive nature of the prescribed drug

e. Documented assessment of the potential for abuse and /or diversion of the prescribed drug,

f. That the Prescription Drug Monitoring Program had been checked prior to issuing the prescription

g. A detailed clinical rationale for the prescribing and the patient must be seen in an in-person examination every three (3) months or every 90 days

h. The definition of "excessive" as contained in this Regulation shall not apply to prescriptions written for a patient in hospice care, in active cancer treatment, palliative care, end-of-life care, nursing home, assisted living or a patient while in an inpatient setting or in an emergency situation

i. Regular urine drug screens should be performed on patients to insure the patient is taking prescribed medications and is not participating or suspected in participating in diversion or abuse of non-prescribed medications. The treatment of chronic pain shall be consistent with the CDC guidelines as they relate to baseline drug testing, and at least annual follow up testing as warranted for treatment

j. A pain treatment agreement must be signed and reviewed by the patient when initiating chronic opioid therapy. This agreement should discuss the following: informed risk and addictive nature of prescribed medications, outline the specific expectations between patient and physician, informed consent for periodic urine drub screening and random pill counts with urine screening as well as the provisions for termination of opioid therapy.

There is more, of course, and it's all pertinent information on things like checking the PDMP, newly required CME, etc. **Read the rule in full at armedicalboard.org.**

Omar Atiq, MD

Clarification: A Note About Limits

Last month, we published a quote from Dr. Smith that read "… the new regulations limit the first prescribing of opioids for acute pain to seven days or less."

To clarify, the regulations call not for a "limit," but for "documented justification." Dr. Smith was referring to the section of 2.4 that addresses acute pain. That section states, "for the treatment of acute pain, *excessive* is further defined as an initial medical justification for more than seven (7) days **without** detailed, documented medical justification in the medical record. If the patient requires further prescriptions, they must be evaluated in regular increments with documented medical justification for continued treatment in the medical record."

"You can write it for *30* days if you show a detailed, documented justification in the medical record. There's no ambiguity in that," explained O'Dwyer. "However, physicians don't need to 'just come up with a justification and you're good.' Clearly, the intent of recent legislation and the consensus of anybody involved in this fight, is not for doctors to 'keep on keeping on,' Rather, we want them to scale way back and still provide good care for their patients. That said, I don't think this rule is the problem or even the reason for the dramatic prescribing adjustments that we've seen. For instance, from Jan. 1-June 30, 2017, and for the same period in 2018, there [were around] 248,000 fewer prescriptions written. [Regulation] 2.4 wasn't even in effect at that point. I know a lot of people are pointing to 2.4 as a reason. That's fine, I think, as long as they're reducing their prescribing."

To Help, Not Hinder

With all of this in mind, physicians should be aware – not afraid – of Regulation 2.4. This from ASMB member Omar Atiq, MD, who was involved in passing the amendments. "The rule was passed because of the opioid crisis in our cities and towns and the rest of our country to see if we could try and reduce the morbidity associated with it," said Dr. Atiq "Arkansas, unfortunately, is one of the states where the prescription of opioids is in the top 10%."

As opposed to being something to confuse physicians or patients, the rule is there to help physicians. "It really CLARIFIES things and essentially helps a physician follow certain steps when they prescribe higher doses or longer durations of opioids," he stressed. "It helps them detail in their notes the reason, the rationale, for giving the opioids and helps them make sure that patients are well served by each prescription."

Are you an Arkansas physician who, considering the opioid epidemic and ongoing related work, has recently changed (or is in the process of changing) your opioid prescribing patterns? Are you willing to share, for the good of the order, changes you've made or are making? Contact the author at casey@pennwords.com or David Wroten at AMS (501) 224-8967.

Related Research

1. Shah A, Hayes CJ, Martin BC. **Characteristics of Initial Prescription Episodes and Likelihood of Long-Term Opioid Use** — United States, 2006–2015. MMWR Morb Mortal Wkly Rep 2017;66:265–269. DOI: http://dx.doi.org/10.15585/mmwr.mm6610a1.AMS

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A CLOSER LOOK AT QUALITY

Trauma-Informed Care Needed to Combat ACEs

JANIE GINOCCHIO, MPA, AND DAPHNE GAULDEN, MPA, MPH

Arkansas has the highest percentage of children with at least one adverse childhood experience (ACE), nearly 56 percent compared to an average of 46 percent of children nationally. As many as one in seven children in the state have experienced three or more ACEs.[1] According to the 2016 Behavioral Risk Factor Surveillance System survey, 60 percent of Arkansas adults have experienced at least one ACE. In a quarter of Arkansas counties, more than 20 percent of adults have experienced four or more ACEs.[2]

Research shows that ACEs increase the long-term risks for smoking, alcoholism, drug abuse, depression, heart and liver disease, and a dozen other illnesses and unhealthy behaviors. In the seminal 1998 ACE Study funded by Kaiser Permanente and the Centers for Disease Control and Prevention, Vincent Felitti and his colleagues first identified ACEs. They noted that the mental and/or physical trauma caused by ACEs falls into three categories: abuse (physical, sexual or emotional), neglect and household dysfunction, which includes divorce, parental incarceration, substance abuse, mental illness or exposure to domestic violence.[3]

Most people surveyed in the ACE Study were white, college-educated and middle-aged people who scored from zero to 10 based on the number of ACEs each had. When researchers compared respondents' ACE scores with health insurance claims, they found those people with ACEs were more likely to experience negative health effects.[4] For example, an ACE score of six is associated with a lifespan shortened by 20 years. A person with an ACE score of four is 400 percent more likely to develop chronic obstructive pulmonary disease.[3]

Subsequent ACE surveys with more diverse populations mirrored these results. The surveys examined the role that economic and community factors such as poverty and violence have as ACEs and the protective factors that have the greatest impact on health outcomes.[5]

The current understanding is that ACEs activate a child's stress response system and are a form of developmental trauma. Without protective factors such as a secure attachment to a parent or other adult, the stress response becomes chronic or toxic, which in turn affects the development of the brain and other organs.

Experiencing the mental trauma of severe ACEs may cause patients to have difficulty trusting others, including health care professionals. They may be uncomfortable in a health care setting, which can lead them to be noncompliant with physician directives.6 Efforts to restrict or prohibit unhealthy coping mechanisms such as smoking can escalate feelings of distrust and resistance to medical advice.

Considering that some of Arkansas' most serious health concerns can be linked to individual and community-level trauma, there is a need for well-trained individuals to champion and implement trauma-informed care (TIC) approaches in community-based settings.

TIC is a way of providing services by which health care and human service providers recognize, understand and respond to the effects of mental and emotional trauma in the lives of patients. TIC views the presenting problems as potential symptoms of maladaptive coping. Providers who use TIC can better understand how early trauma shapes a person's fundamental belief about the world and affects lifelong psychological functioning.

According to the Substance Abuse

and Mental Health Services Administration, a program, organization or system that is trauma-informed will be able to:

- Realize the prevalence of trauma and understand potential pathways for recovery
- Recognize signs and symptoms of trauma in clients, families, staff and others involved in the system
- Respond by fully integrating knowledge about trauma into its current policies, procedures and practices
- Actively resist re-traumatization by exposing individuals to triggers without providing the proper support or sensitivity[7]

Health care providers should adopt TIC practices on both organizational and clinical levels. Organizational culture must change to include a focus on amending policies that have the potential to cause trauma for patients and staff, while clinical approaches work to address trauma's effects on individual patients.[6]

The Center for Health Care Strategies (CHCS), a nonprofit policy organization dedicated to improving the health of low-income Americans, is leading a national initiative to advance TIC in the clinical setting. CHCS developed the following key organizational and clinical ingredients for TIC:

ORGANIZATIONAL INGREDIENTS FOR TIC[6]

Engage patients in organizational planning. Provide opportunities for patients who have personally experienced trauma to join a patient engagement committee and help guide efforts for implementing TIC.

Train clinical as well as nonclinical staff members. Create a welcoming, trusting, nonjudgmental environment by training nonclinical staff, including security guards and front-desk workers, on the impact that trauma can have on behavior and how to de-escalate tense situations.

Create a safe physical and emotional environment. Reduce noise levels in waiting rooms and clinical areas to provide a calm, quiet environment. Develop policies and procedures to ensure that patients feel respected.

Prevent secondary traumatic stress in staff. Train staff on how their own ACEs or traumatic experiences can be triggered while interacting with patients and how to perform self-care to reduce burnout.

Hire a trauma-informed workforce. Use behavioral interviewing techniques to look for qualities in job candidates such as empathy, nonjudgment and collaboration.

CLINICAL INGREDIENTS FOR TIC[6]

Engage patients in the treatment process. Empower patients by involving them in decision-making and development of their care plan, rather than telling them what will be done.

Screen for trauma. Use validated screening tools such as the Life Event Checklist (www.integration.samhsa.gov/clinical-practice/life-event-checklist-lec.pdf) or the Abbreviated PCL-C PTSD checklist for civilians (www.integration.samhsa.gov/clinical-practice/Abbreviated_PCL.pdf).

Train staff in trauma-specific treatment approaches. Identify and train staff using an evidence-based model that best meets the needs of your organization's care model and population served.

Engage referral sources and partner organizations. Work with community partners and within a system of care to develop a robust trauma-informed referral network.

The Arkansas Adverse Childhood Experiences and Resilience Workgroup, a cross-sector collaboration working to prevent and address the negative impacts of ACEs, is developing trainings for providers interested in adopting TIC in their practices. For more information, contact Janie Ginocchio at jginocchio@afmc.org. ▲

Ms. Ginocchio and Ms. Gaulden are program and policy analysts at AFMC and coordinate the Arkansas Adverse Childhood Experiences and Resilience Workgroup.

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Epidemiological Analysis of Orbital Masses at Tertiary Centers in Central Arkansas

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Keywords: orbital, tumor, mass, histopathology

Abstract

Orbital tumors and simulating masses may present at any age and represent a variety of both benign and malignant lesions. It is important to index the frequency of orbital lesions in Arkansas to assist clinicians in the region with the formation of differential diagnosis and expedite appropriate referrals and treatment of patients. This study looks at the incidence of orbital tumors and simulating masses with histopathological confirmation seen at tertiary institutes in central Arkansas in patients of any age over a 15-year period. This study reports the most common orbital masses in age groups 0-18, 19-39, 40-64, and 65 and over.

Orbital tumors and simulating masses may present at any age and represent a variety of both benign and malignant lesions. Different types of orbital lesions can affect the orbit and surrounding structures. These masses can cause ptosis, proptosis, globe displacement, vision loss, altered ocular motility, and some can be life-threating.[1,2,3]

Several studies have reported on the frequencies of orbital tumors, yet determination of a true incidence is difficult due to variability of methods across published studies.[1] Additionally, many studies lack complete histopathological confirmation.[1,2] Reported data of orbital lesions vary between series, depending on the population studied. Some studies have looked at only certain age groups or geographical area, while others used diagnoses based off of clinical, radiographic, and/or histopathologic findings. [1,2,3]

Table 1

Category	Number of Patients	Percent
Females	81	57%
Males	61	43%
Category	**Number of Patients**	**Percent**
Caucasian	106	75%
African American	25	18%
Hispanic	7	5%
Asian	1	1%
Indian	1	1%
Unknown	2	1%

The goal of this study was to determine the incidence of different types of histopathologically confirmed orbital tumors and simulating masses seen at tertiary institutes in central Arkansas in patients of any age over a 15-year period. It is the authors' goal that information from this study regarding incidence and phenotype of particular orbital masses will serve as a reference for physicians in central Arkansas as they counsel patients and provide appropriate work up and referral.

Methods

Upon approval by the UAMS IRB, a retrospective search of histopathologic diagnoses from orbital masses was conducted at both UAMS and Arkansas Children's Hospital. Cases were identified by search of CPT codes for orbital tumors and simulating masses and confirmed by documented histopathologic diagnosis. Search was conducted between April 1999 and April 2015 and included patients of all ages.

Upon compilation of cases following the above screen, strict inclusion and exclusion criteria were applied. For inclusion into this study, the lesion had to be an orbital mass, tumor, or simulating lesion involving the orbit in which its final diagnosis was made by histopathological biopsy. Lesions were excluded if

Table 2

Types of Orbital Mass	Number of Patients	Percent
Cystic Lesions	36	25.4%
Inflammatory Lesions	19	13.4%
Lacrimal Gland Lesions	19	13.4%
Lymphoid or Leukemic Lesions	17	12.0%
Vasculogenic Lesions	14	9.9%
Secondary Tumors from Adjacent Structures	10	7.0%
Lipocytic or Myxoid Lesions	9	6.3%
Miscellaneous	6	4.2%
Osseous/Fibro-osseous Lesions	3	2.1%
Metastaric Lesions	3	2.1%
Carcinoma	2	1.4%
Peripheral Nerve Lesions	2	1.4%
Fibrocytic Lesions	1	0.7%
Sarcoma	1	0.7%

Table 3.1

Orbital Lesions Found in 0-18 Years of Age (N=49)	Number of Lesions	Percentage
Dermoid Cyst	27	55.1%
Langerhans Cell Hystio	3	6.1%
Cyst	1	2.0%
AML	1	2.0%
Epidermal Inclusion Cyst	1	2.0%
Cellular Hemangioma	1	2.0%
Chronic Inflammation	1	2.0%
Dermolipoma	1	2.0%
Eidermal Cyst	1	2.0%
Keratin-Filled Cyst	1	2.0%
Lacramial Gland with Chronic Inflammation	1	2.0%
Lipoma	1	2.0%
Lymphoblastic Lymphoma	1	2.0%
Lymphoblastic Malformation	1	2.0%
Mature Teratoma	1	2.0%
Phakomatous Choristoma	1	2.0%
Prolased Orbital Fat	1	2.0%
Rhabdomyosarcoma	1	2.0%
Chondrofibroma	1	2.0%
Neurofibroma	1	2.0%
Neurofibromatosis	1	2.0%

they lacked histopathological biopsy and if the lesion was limited to the eyelids or eyeball without orbital involvement. The number and percentage of each subtype of neoplastic and non-neoplastic disease was calculated.

Results

During the 15-year period from 1999 to 2015, there were 273 cases that matched the initial CPT search, but only 142 met inclusion criteria for this study. Demographics of our study are shown in Table 1, demonstrating that of the orbital lesions investigated, 57% were found in females, and 75% of all the lesions were found in Caucasian patients.

The number and percentage of lesions in each major category are shown in Table 2. The most common type of orbital lesions presenting in Arkansas were cystic lesions, accounting for 25.4%, followed by inflammatory lesions (13.4%) and lacrimal gland lesions (13.4%).

The demographics and orbital mass breakdown by age group are shown in Tables 3,4,5 and 6. Amongst pediatric patients less than the 18 years, the most common orbital lesion was a dermoid cyst, accounting for 55.1% of all masses within this age group. Orbital lesions occurred more frequently in Caucasians (80%) and in males (53%) within the 0-18 age group. The most common orbital location in this age group was the superotemporal region.

In the 19-to-39-year-old age group (Table 4), the most common orbital lesions were the dermolipoma (8.3%) hemangiopericytoma (8.3%) and orbital abscesses (8.3%). Orbital lesion occurred more frequently in Caucasians

Table 3.2

Gender Breakdown of Orbital Lesions Found in Ages 0-18	Number	Percentage
Females	23	47%
Males	26	53%

Table 3.3

Race Breakdown of Orbital Lesions Found in Ages 0-18	Number	Percentage
Caucasian	39	80%
AA	6	12%
Hispanic	4	8%

Table 3.4

Laterality Breakdown of Orbital Lesions Found in Ages 0-18	Number	Percentage
Right	26	53.1%
Left	23	46.9%

Table 3.5

Orbital Location of Orbital Lesions Found in Ages 0-18	Number	Percentage
Superotemporal	14	28.6%
Temporal	13	26.5%
Unknown	9	18.4%
Nasal	5	10.2%
Superior	3	6.1%
Inferior	2	4.1%
Superonasal	2	4.1%
Inferotempral	1	2.0%

(62.5%) and in females (70.8%). The most common orbital location in this age group was the lacrimal gland.

In the 40-to-64-year-old age group (Table 5), there was not one overall common lesion. Orbital lesion tended to occur slightly more frequently in females (56.8%) and in Caucasians (68.2%). The lacrimal gland and superotemporal region of the orbit were the most common location for orbital lesions in this age group.

In the 65-plus age group (Table 6), the most common orbital lesion was a squamous cell carcinoma making up 16% of lesions. Orbital lesion occurred more frequently in Caucasians (88%) and in females (64%). The lacrimal gland and temporal region of the orbit were the most common location for orbital lesions in the 65-plus age group.

Discussion

The authors included all orbital tumors and simulating masses seen at two tertiary institutes in Arkansas over the last 15 years with histopathologi-

> Continued on page 112.

Table 4.1

Orbital Lesions Found in Ages 19-39 (N=24)	Number of Lesions	Percentage
Dermolipoma	2	8.3%
Hemangiopericytoma	2	8.3%
Abcess	2	8.3%
AVM	1	4.1%
Blastocystis	1	4.1%
Cavernous Hemangioma	1	4.1%
Chronic Dacroadenitits	1	4.1%
Conjunctival Cyst	1	4.1%
Chronic Fibrosingdacryoadenitis	1	4.1%
Dermoid Cyst	1	4.1%
Epidermal Cyst	1	4.1%
Epidural Abcess	1	4.1%
MALT Lymphoma	1	4.1%
Metastaic Mucoepidermoid Carcinoma	1	4.1%
Pleomorphic Adeoma	1	4.1%
Recurrent Lymapthic Malformation	1	4.1%
Sarcoidosis	1	4.1%
Squamous Cell Carcinoma	1	4.1%
Small Non-necratizing Granuloma	1	4.1%
Solitary Fibrous Tumor	1	4.1%
Venous Malformation	1	4.1%

Table 4.2

Gender Breakdown of Orbital Lesions Found in Ages 19-39	Number	Percentage
Females	17	70.8%
Males	7	29.2%

Table 4.3

Race Breakdown of Orbital Lesions Found in Ages 19-39	Number	Percentage
Caucasian	15	62.5%
AA	5	20.8%
Hispanic	3	12.5%
Indian	1	4.1%

Table 4.4

Laterality Breakdown of Orbital Lesions Found in Ages 19-39	Number	Percentage
Right	16	66.6%
Left	7	29.1%
Bilateral	1	4.1%

Table 4.5

Orbital Location of Orbital Lesions Found in Ages 19-39	Number	Percentage
Lacramal Gland	5	20.8%
Superotemporal	4	16.7%
Lateral	3	12.5%
Medial	2	8.3%
Inferotemporal	2	8.3%
Unknown	2	8.3%
Intraconal	2	8.3%
Superomedial	2	8.3%
Inferior	1	4.1%
Superior	1	4.1%

cal confirmation, and, studied the incidence of these lesions. The most common lesion types were cystic lesions, comprising 25.4% of all lesions. This finding was consistent with similar studies.[2] The next most common lesions in our study were inflammatory lesions, followed by lacrimal, and lymphoid or leukemic lesions.

Of specific interest in this study was the characterization of tumor type by age. For the zero-to-18-year-old age group, the most common orbital lesion was the dermoid cyst. This is consistent with data reported in studies conducted by both Kennedy and Rootman.[2,4,7] Langerhans cell histiocytosis was another common orbital lesion in the pediatric age group making up 6.1% of lesions. This pathology is much more common in pediatric patients and thus is an important characterization in the work up of pediatric patients with orbital masses. It has been found that up to 22% of the orbital Langerhans cell histiocytosis in pediatric patients are malignant, reinforcing the need for prompt diagnosis and initiation of work up[9].

In the 19-to-39-year-old age group, the frequency of orbital masses was much more homogenous. Of note, it is surprising that a hemangiopericytoma was one of the most common lesions in this age group in our series because it is a relatively rare lesion as reported in the literature. The orbit is a rare location for this tumor, with hemangiopericytoma making up 0.8% to 3% of all primary orbital tumors.[10] However, there are only two of these in the whole study and they happened to both fall in this age group, and this is also the age group that had the least amount of lesions. When considering all age groups, Hemangiopericytomas only make up 1.4% of the masses found within the study; this is within the range reported in the literature. Within this age group, orbital lesions occurred more frequently in females (70.8%).

The 40-to-64-year-old group had a wide array of orbit lesions with similar incidence of pathology. However, different types of lymphoid lesions made up the bulk of the lesions in this group. Lymphomas have been reported as the most frequently occurring malignant orbital tumors in adults[6], which is consistent with our findings.

In the 65-plus group, the most common orbital lesion was squamous cell carcinoma, which has been reported as the most frequent secondary

Table 5.1

Orbital Lesions Found in Ages 40-64 (N=44)	Number of Lesions	Percentage
B-Cell Lymphoma	2	4.5%
Basal Cell Carcinoma	2	4.5%
Cavernous Hemangioma	2	4.5%
Dacroadenitis	2	4.5%
Extranodal Marginal Zone Lymphoma	2	4.5%
Pseudotumor	2	4.5%
Pyogenic Granuloma	2	4.5%
MALT Lymphoma	2	4.5%
Plemorphic Adenoma	2	4.5%
Adenoid Cystic Carcinoma	1	2.3%
AVM	1	2.3%
Carcinoma	1	2.3%
Conjunctival Cyst	1	2.3%
Dermolipma	1	2.3%
Epithelial Cyst	1	2.3%
Fibrous Dysplisa	1	2.3%
Graves Orbitopathy	1	2.3%
Hematic Cyst Chol	1	2.3%
Herniated Subconj Fat	1	2.3%
Idiopathic Sclerosing Fibrosis	1	2.3%
Idiopathic Sclerosisng Orbital Inflammation	1	2.3%
Inflammatory Condition	1	2.3%
Lacrimal Gland Cyst	1	2.3%
Lymphoid Hyperplaisa	1	2.3%
Mature Small B Cell Lymphoma	1	2.3%
Melanoma	1	2.3%
Metastic Adenocarcinoma	1	2.3%
Metastic Carcinoma	1	2.3%
Nt/T Cell Lymphoma	1	2.3%
Prolapsed Orbital Fat	1	2.3%
Squamous Cell Carcinoma	1	2.3%
Shwannoma	1	2.3%
Ted Proptosis	1	2.3%
Thrmobosed Varix	1	2.3%
Venous Malformation	1	2.3%

orbital malignancy.[2,8] However, when considering all subtypes of lymphomas, this general category makes up 28% of all the orbital lesions within this age group, making this the most common orbital lesion, which is consistent with other studies.[6] According to Demetri et al, 63% of all orbital tumors in the senior adult population are malignant; primary, locally invasive, or metastatic. Thus, orbital lesions in the adult population need urgent work up and proper referral.

Table 5.2

Gender Breakdown of Orbital Lesions Found in Ages 40-64	Number	Percentage
Females	25	56.8%
Males	19	43.2%

Table 5.3

Race Breakdown of Orbital Lesions Found in Ages 40-64	Number	Percentage
Caucasian	30	68.2%
AA	12	27.3%
Hispanic	2	4.5%

Table 5.4

Laterality Breakdown of Orbital Lesions Found in Ages 40-64	Number	Percentage
Right	18	40.9%
Left	23	52.2%
Bilateral	3	6.8%

Table 5.5

Orbital Location of Orbital Lesions Found in Ages 40-64	Number	Percentage
Lacrimal Gland	7	15.9%
Superotemporal	7	15.9%
Superior	6	13.6%
Unknown	6	13.6%
Temporal	6	13.6%
Medial	3	6.9%
Inferomedial	2	4.5%
Inferior	2	4.5%
Intraconal	2	4.5%
Superiomedial	2	4.5%
Inferotemporal	1	2.3%

Presenting a large regional investigation of orbital mass incidence in the state of Arkansas has limitations. Firstly, this study is a chart-based retrospective review with retroactively applied review of prior patient information. Additionally, initial screening of patients was by CPT code, which could have excluded improperly labeled patients and pathology. Inclusion of only histopathologically proven orbital masses likely skews the data presented here towards lesions that were more likely (whether by size or symptoms) to be surgically resected. Finally, this study is limited by its regional nature and may not represent incidence in other areas of the U. S. and worldwide.

In summary, this study was undertaken to determine the number and percentage of various lesions seen at tertiary centers in central Arkansas.

> Continued on page 114.

Table 6.1

Orbital Lesions Found in Ages 65 Years or Older (N=25)	Number of Lesions	Percentage
Squamous Cell Carcinoma	4	16.0%
Large B-Cell Lymphoma	2	8.0%
Florid Non-Nec Granulomatous Inflammation	2	8.0%
Extranodal Marginal Zone Lymphoma (Malt Type)	2	8.0%
Benign Palisading Granuloma	1	4.0%
Connective Tissue with Inflammation	1	4.0%
Diffuse Large B Cell Lymphoma	1	4.0%
Fat And Lymphocticin Infiltrate	1	4.0%
Fibrous Tissue	1	4.0%
Graves Ophthalmopathy	1	4.0%
Follicular Lymphoma	1	4.0%
Marginal Zone Lymphoma	1	4.0%
Metastaic Adenocarcinoma	1	4.0%
Papilloma	1	4.0%
Plasma Cell Myeloma	1	4.0%
Sebaceous Carcinoma	1	4.0%
Steatoblepharn	1	4.0%
Venous Malformation	1	4.0%
Wegeners Granulomatosis	1	4.0%

Table 6.2

Gender Breakdown of Orbital Lesions Found in Ages 65 Years of Age or Older	Number	Percentage
Females	16	64%
Males	9	36%

Table 6.3

Race Breakdown of Orbital Lesions Found in Ages 65 Years of Age or Older	Number	Percentage
Caucasian	22	88%
AA	2	8%
Asian	1	4%

Table 6.4

Laterality Breakdown of Orbital Found in Ages 65 Years of Age or Older	Number	Percentage
Right	13	52.0%
Left	9	36.0%
Bilateral	3	12%

Table 6.5

Orbital Location of Orbital Lesions Found in Ages 65 Years of Age or Older	Number	Percentage
Temporal	5	20.0%
Lacrimal Gland	5	20.0%
Unknown	4	16.0%
Superior	4	16.0%
Medial	2	8.0%
Superotemporal	1	4.0%
Inferotemporal	1	4.0%
Superomedial	1	4.0%
Inferotemporal	1	4.0%
Inferomedial	1	4.0%

The incidence of different subtypes of orbital lesions seen in Arkansas may assist clinician in the region in formulating differential diagnosis in a patient presenting with orbit-related signs and symptoms.

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CASE STUDY

Multiple Sclerosis-Like Neurologic Symptoms In a Rheumatoid Arthritis Patient On Etanercept

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Keywords Altered mental status, diplopia, drug adverse effect, biologics, TNF alpha antagonist

Abstract

We report the case of a 35-year-old gentleman who developed fatigue, cognitive changes described as "fogginess," unilateral headache, same-sided facial numbness and diplopia on left lateral gaze, while on the tumor necrosis factor alpha (TNF-α) antagonist etanercept for management of long-standing rheumatoid arthritis. MRI of brain, MR angiography of cerebral circulation, and analyses of cerebrospinal fluid (CSF) were normal. No oligoclonal bands were detected in the CSF. C reactive protein and sedimentation rates were normal. Lyme titer was positive and 43 and 66 kDa IgG antibodies were detected. The decision was taken to stop etanercept. In addition, the patient was treated with ceftriaxone for presumed Lyme disease. Though no frank evidence of demyelination was obtained, the symptom complex resembled presentation of multiple sclerosis. Tumor necrosis factor (TNF)–α inhibitors belong to a class of disease-modifying antirheumatic drugs that have revolutionized the treatment of inflammatory rheumatologic disorders. Despite their clinical benefit in rheumatologic conditions, TNF-α inhibitors have been implicated in the development of CNS and peripheral nervous system disorders. Clinical alertness shall help to detect and avoid cataclysmic neurologic adverse outcomes related to anti-TNF–α therapy.

Introduction

Biologics, targeting and antagonizing a specific biologic pathway, are a common class of medications in current medical care. These medications are considered relatively safe and have well-defined side effect(s). However, unpredictable adverse effect(s) (A/Es) may arise, thus necessitating alertness and clinical suspicion during their clinical use. Here we describe such an associative condition in which an adult male patient with long-standing rheumatoid arthritis on chronic disease control with the TNF–α (tumor necrosis factor alpha) antagonist etanercept developed sub-acute altered mental status, fatigue and unilateral headaches, facial pain, and diplopia on lateral gaze.

Case report

A 35-year-old, well-built male individual with a pleasant personality, and history of polyarticular joint disease due to seronegative rheumatoid arthritis for the last 16 years was admitted to our hospital for evaluation of persistent headache and visual symptoms. The patient initially presented with left unilateral daily headache around the left eye radiating to the back of the left occiput described as a squeezing, pressure sensation; left-sided facial pain and numbness, and left-sided diplopia for four-to-six-week duration. His primary care physician started him on Fioricet and nortriptyline, which did not improve the symptoms. The headache seemed to be worse in the night. He denied any chest pain, nausea, vomiting, or cough. He was initially provided with a provisional diagnosis of migraine and treated accordingly. However, there was no improvement of symptoms. There was associated cognitive impairment and emotional lability, described by the subject as low energy, decreased concentration, and "fogginess," which prompted for hospital admission for evaluation of altered mental status.

The patient had a long-standing history of inflammatory polyarthritis. He was on chronic steroid therapy and a presentation consistent with sero-negative symmetric inflammatory polyarthritis. Alongside, the patient had co-existing proximal muscle weakness and elevated CPK, thus inflammatory myopathy being in the differential. Earlier, in August 2013, prednisone was stopped. The patient was bridged with Medrol, which was gradually tapered and then started on Enbrel (etanercept) for management of joint disease. The patient had no known drug allergies (only documented allergy was to cashew), no rashes or psoriasis.

The patient was on etanercept for approximately the last 28 months. During his hospital admission for evaluation of these emergent conditions including diplopia, detailed eye examination was performed. His fundus examination was normal. Cranial nerves examination revealed full extraocular movements, but diplopia on left gaze. Using a red glass test, it localized the abnormal image to abduction of the left eye, likely involving dysfunction of the sixth cranial nerve. Facial sensation reported a decrease in pinprick over V1 and V2 on the left side. Motor examination revealed full power in the upper and lower extremities with intact reflexes. The neurologic symptoms were presumed to be related to the use of etanercept and a decision was taken to stop the

biologic agent. The symptoms improved, and he did not have any headache, but he still complained of diplopia and fatigue two months after the hospital course. Neurological examination including cranial nerve examination was normal two months following discharge. Behavioral evaluation at this time revealed normal mood and affect, language, thought and cognition.

During the hospital stay, notable labs included: (i) an elevated total bilirubin (1.08 U/L) and liver enzymes (AST 51 U/L, ALT 169 U/L); (ii) a low HDL cholesterol (13.5 mg/dl); other lipid parameters within normal limits (LDLc 83.7 mg/dl, cholesterol 114 mg/dl, triglyceride 77, cholesterol/HDL ratio 5.6); (iii) C reactive protein (CRP) was non-elevated at 0.29 mg/L; (iv) WBC count was 12.1 k/UL on day of admission (Neutrophils 87% and lymphocyte 6%); (v) D-dimer was unelevated at 0.26 ug/ml; (vi) the sedimentation rate was 0 ml/hr; (vii) negative ANA titer; (viii) Notable parameters in comprehensive metabolic panel (CMP) revealed glucose 138 mg/dl, HbA1C 5%, Calcium 9.8 mg/dl, Magnesium 2.2 mg/dl, TSH 0.66 UlU/ml.

Clear CSF was obtained by lumbar puncture (LP) performed by aseptic procedures under anesthesia. Notable finding during CSF examination was slightly elevated protein (50) and glucose (81). No oligoclonal band was detected by isoelectric focusing (IEF). Oligoclonal bands are usually present in the CSF in greater than 85% patients with the demyelinating disease multiple sclerosis. It may also be detected in brain tumor, infarction, CNS lupus, inflammatory polyneuropathy, and sub-acute sclerosing panencephalitis. CSF cultures were normal.

HIV1 and 2 IgG antibodies were undetected. RPR was non-reactive. Lyme antibody was detected (1.84; >1.10 is considered as positive). Further Lyme-specific antibodies were evaluated by western blotting. 41 kDa and 66 kDa IgG bands were detected; all other bands for IgM and IgG were negative.

Myelin basic protein was less than 2 mg/L. CSF IgG was 2.3 mg/dl, albumin CSF 23.8 mg/dl, IgG serum 773 and albumin serum 3.5 g/l, leading to IgG index of 0.44 (normal 0.66).

Routine MRI of brain without contrast and with Magnevist did not reveal any acute intracranial abnormality or abnormal enhancement. A few tiny foci of increased T2 and FLAIR signals was seen scattered throughout the cerebral hemisphere, which is a nonspecific finding seen in chronic migraine headaches. However, these findings may also be indicative of demyelination. There was no restricted diffusion to suggest infarction, no extra-axial collection, and normal vascular flow voids of the skull base. 3D time-of-flight magnetic resonance angiography (MRA) of the intracranial arterial vessels showed normal patterns of the vascularity of the circle of Willis, with a normal variation of the right posteroinferior cerebellar artery (PICA). Vertebral and basilar arteries showed normal dimension bilaterally without aneurysm.

The remainder of the hospital course involved insertion of a PICC for administration of ceftriaxone for suspected Lyme disease, though this consideration was low on the differential. USG abdomen revealed distended gall bladder with several gall stones. Blood culture during the hospital course had shown no growth.

The gentleman in discussion is a fitness instructor, lives at home with his wife, and has a pet dog. He denied any history of drug or tobacco use. Though numerous joint involvement due to rheumatoid arthritis, our patient is a lifestyle coach and actively participates in gym activities and golf. Important past medical history includes herpes zoster involving the face about five years ago. The patient did not remember the sidedness, although his wife reported that it might have been on the right side.

Discussion

The current report presents an associative condition of use of the biologic agent anti-TNF antagonist etanercept and development of diplopia and other neurologic symptoms resembling the heterogeneous presentation of multiple sclerosis. These could have resulted from the effects of etanercept. The only correlative evidence we can offer in support of this association is that the patient's symptoms considerably improved after cessation of the medication.

The role of cytokines in maintenance of myelination is being increasingly appreciated. Thus, cytokine antagonists may cause demyelination, involving both cranial and peripheral nerves.[1,2] We ruled out preliminary demyelinating disorders like multiple sclerosis by negative oligoclonal bands as well as normal CSF IgG index. The third, fourth and sixth cranial nerves traversing through the cavernous sinus derives its blood supply from adjacent vessels.[3] MR angiography revealed intact basilar vasculature, as well as the internal carotids and normal cavernous sinuses. The lipid parameters for our patient was also normal. The likelihood that an acute or acute-on-chronic vascular disorder resulting from metabolic dysfunction affecting the nerve supply of the cranial nerves supplying the extraocular muscles, leading to the visual disturbances, was likely low. Two months after the episode, clinical evaluation demonstrated normal function of cranial nerves, though the left pupillary reaction to light was somewhat sluggish.

Whether etanercept contributed to cognitive deficits cannot be predicted by the information obtained from our patient. The patient had no evidence of any cognitive deficit two months after the initial episode. The significance of the periventricular T2/FLAIR signals also remains unknown.

Earlier, a single report has identified extraocular myopathy leading to painful diplopia after the use of etanercept. Our report delineates a similar associative condition, though we remain unsure of whether demyelinating nerve disease involving the cranial nerves supplying the extra-ocular muscles or a myopathy per se was the cause of the development of the visual disturbances. The patient had other neurologic features, including headache and transient cognitive decline, without any frank neurovascular abnormality detected by imaging and routine neurologic evaluation. It is prudent to be aware about such situations, which may help in continued clinical care. MRI did not reveal any frank demyelination.

Though precision medicine has ushered in newer agents for pharmacotherapy catering to novel treatments for a wide variety of diseases, use of these agents should always be with caution. The present case highlights this issue. Complete information from package insert and other literature should be obtained prior to using these medications. Anti-TNF alpha based medications is now common pharmacologic drugs used for many autoimmune and inflammatory conditions, including arthritides of diverse etiologies. Anti TNF–α drugs have been associated with multiple sclerosis, optic neuritis, acute transverse myelitis, progressive multifocal leucoencephalopathy, and acute and chronic inflammatory demyelinating polyneuropathy.[1-2, 4-11] Precise neuroimmune interactions are not known. Despite high TNF–α levels in multiple sclerosis plaques and the cerebrospinal fluid, anti-TNF–α drugs seem to trigger MS and worsen its course.[10-12]

The development of neurological disorders in patients on anti-TNFalpha medications is stochastic in nature.[13-15] A recent study has shown that a certain type of single nucleotide polymorphism (SNP) on the TNF receptor increases susceptibility to demyelinating disorders, the mutated receptor itself acting in aberrant signaling leading to de-

velopment of multiple sclerosis-like symptoms. This SNP, (rs1800693) however, does not occur in rheumatoid arthritis or other autoimmune diseases like psoriasis or Crohn's disease.[14] This SNP, however, predisposes to primary biliary cirrhosis.[16] It has been proposed that this SNP may predispose to increased demyelination upon exposure to TNF antagonists.[14] Routine genotyping for these predisposing SNPs may not be clinically feasible.

Our patient continues to have multiple joint problems, including shoulder and hip pain, and frequent knee joint problems. Our patient was started on abatacept as an alternative biologic, after discussion of the possibility of use of tocilizumab, tofacitinib, and rituximab. The continued need for use of these biologics also raised suspicion for paraneoplastic condition, which is currently being evaluated.

In summary, the present case highlights that use of TNF–α agent etanercept may cause multiple sclerosis-like symptoms including fatigue and personality changes, sensory deficits, and neuromyopathy, including diplopia due to involvement of the cranial nerves supplying the extraocular muscles. Aggressive identification of evolving symptoms shall prevent adverse neurologic outcomes.

Addendum: The association and clinical presentation shall be reported to the FDA Medwatch.

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OBITUARIES

HOT SPRINGS – **William Robert "Bill" Mashburn, MD**, passed away August 18, 2018. Dr. Mashburn graduated from the UAMS College of Medicine in 1960 with a doctorate of medicine. He interned at the old Baptist Hospital where he was named the "intern with the best bedside manner" by the hospital staff. Dr. Mashburn began practicing medicine in Hot Springs, Ark., where he joined in practice with Dr. Louis G. Martin. He also practiced family medicine before retiring in 1990. He served as county coroner of Garland County for 16 years, prior to retiring from that office in 2000. Additionally, Bill served as chief of staff at Park Medical. He was a member of the Arkansas Medical Society and the AMS Fifty Year Club.

ADONA – **Damon George Harkey Martin, MD,** passed away September 2, 2018. Dr. Martin attended Arkansas Tech University, Harding University, and the UAMS College of Medicine, where he graduated in 1956 with a doctorate of medicine. After spending a short time in Salem, Ark., practicing medicine, Dr. Martin returned in the fall of 1957 to Yell County. In 1967, Dr. Martin's Brother-in-Law George Tippin helped construct his medical clinic in Ola, where Dr. Martin treated patients until very recently. He was a member of the Arkansas Medical Society and a member of the AMS Fifty Year Club.

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