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Understanding the Fine Print: The Who, When, And What To Do About ARIA in Patients with A lzheimer's Disease - Emergency Medicine Module

Announcer:
Welcome to CME on ReachMD. This activity entitled, Understanding the Fine Print: The Who, When, and What to do About Amyloid-Related Imaging Abnormalities in Patients with Alzheimer's Disease, Emergency Medicine Module. This activity is jointly provided by Medical Education Resources, or MER, and Efficient, LLC, and is supported by an educational grant from Lilly.

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Dr. Galvin:
Hello, my name is Dr. James Galvin and welcome to the Emergency Medicine Module of the Understanding the Fine Print: The Who, When, and What to do About Amyloid-Related Imaging Abnormalities in Patients with Alzheimer's Disease. This activity is part of a series of six distinct activities, each targeting the commonalities and unique aspects of ARIA recognition and management across four specialties: neurology, radiology, emergency medicine, and primary care. In part one, our panel of diverse specialists gave a background of the key features and implications of ARIA that are relevant to clinicians across all these specialties. In this module we'll focus on the unique aspects of ARIA irrelevant to how and why this effect may present to emergency medicine. To help us with this discussion, I'd like to welcome Dr. Christopher Carpenter, Professor of Emergency Medicine at Washington University School of Medicine, and Dr. Gloria Chiang, Associate Professor of Clinical Radiology at Weill Cornell Medical College. Thank you both so much for being here.

Dr. Chiang:
Hi, everyone. Nice to see you again.

Dr. Carpenter:
Hi. Thank you for continuing this conversation.

Dr. Galvin:
All right. So we're going to talk about ARIA recognition and management, and really focusing on the role of emergency medicine. So a couple of topics, we're going to recognize the clinical presentation in the ED, appropriate management in the initial phase of ARIA where applicable, and we'll talk about the accurate and efficient communication with the healthcare team. So we're going to do this by going through a case presentation. So let's meet our patient.

It's a 71-year-old male presenting to the ED to headache and gait difficulties. He has a history of hyperlipidemia, hypertension, and mild cognitive impairment due to AD, so MCI. And his medications are lecanemab 10 milligrams per kilogram I.V., and he got his sixth dose seven days prior to the ED visit. He's also on lisinopril and simvastatin. Now, and when we think about the clinical signs and symptoms of ARIA, about 26% of ARIA is symptomatic, and most of those symptoms are going to be revolving around headache. They don't have - people have confusion or altered mental status, dizziness, vertigo, nausea, vomiting. Seizures are only going to occur in about 0.4% of individuals. So - and the symptoms we typically characterize as mild symptoms, the headache, the confusion, the dizziness, the moderate and - moderate to severe, with severe being the visual disturbance or visual impairment, and seizures.

So Chris, take it away and talk - let's talk about this a little bit.

Dr. Carpenter:
Yeah, so our 71-year-old patient who's just received his sixth dose of the lecanemab comes in with headache and gait disturbance, recognizing that he's got this new dementia therapeutic onboard, is going to need to raise a trigger for our emergency medicine colleagues to think about some of these other symptoms, to ask about them. Is there an acute alteration of mental status? Is there associated dizziness? Are there GI symptoms. Are their focal neurologic findings that go along with this? And visual disturbances, seizures, things that we need to be asking the patient and the care partner who accompanies them to the emergency department about. The American College of Emergency Physicians has a clinical policy for headache. And that policy was written in 2019. It's probably going to need to be updated to include this as a potential diagnostic paradigm in the old model. But we don't, in this presentation, want to get into anchoring bias because we're talking about a particular diagnostic condition in these patients. Headache is extremely common in the ED. In fact, it's about 4.5% of ED visits. And we really lack, at this stage, diagnostic research for this condition of ARIA to quantify the incidence of ARIA as etiology of headaches and gait disturbance, and to really establish our pretest probability. We're going to need that research in the years ahead to be able to quantify sensitivities and specificities, as well as to assess how well physicians in real-world settings, based upon Gestalt and actual patient encounters, can begin to recognize this condition, and think about getting the appropriate imaging and conveying those concerns to radiology to look for the findings.

Dr. Galvin:
So, Gloria, let's talk about the differential diagnosis.

Dr. Chiang:
Yeah, I mean, as Chris mentioned, a lot of the symptoms of ARIA can actually mimic other neurological disease processes. So some of the symptoms that were mentioned, they can be seen in acute ischemic stroke, for example, we can see them with subarachnoid hemorrhages, and we can see them with PRES, which is posterior reversible encephalopathy syndrome, commonly seen with people with high blood pressure, for example.

Dr. Galvin:
And you know, if someone walks in who's confused, dizzy, headache, and unsteady on their gait, you know, all of these things probably are running through our minds as to what's going on with this patient. So there's a lot of work the ED has to do before, you know, we kind of decide what's the next step. And so I think working together is going to really help us try to sort through this issue.

Dr. Chiang:
And another notable consideration is that anti-thrombotic thrombolytic therapies actually require caution, because as you recall, we talked about how the ARIA-H, the ARIA hemorrhagic form, you can have microhemorrhages and siderosis, which is basically blood products or hemorrhage within the brain. And so you could risk giving them increasing hemorrhage in the brain.

Dr. Galvin:
So Chris, you know, let's talk about this, some of the differentials and how you're going to sort through this.

Dr. Carpenter:
And there's some science here to talk about as well from the ED patient population perspective. One consideration Gloria just mentioned was acute ischemic stroke. And the findings that we look for are acute onset of hemiparesis, including facial paresis, visual changes, or dysphasia, or dysarthria. And vision changes, we already talked about can be one of the features of ARIA. Subarachnoid hemorrhage we think about typically in the setting of acute onset of severe headache. Nausea and vomiting, we also think about subarachnoid hemorrhage. And subarachnoid hemorrhage we also think about in the setting of acute onset severe headache, but we think also about things like migraine or vascular dissection that also crosses our diagnostic thought process.

And then the posterior reversible encephalopathy syndrome. We look for uncontrolled hypertension, a defining feature of that, in conjunction with altered mental status, seizures, and non-localized headaches. We'll ask the council ARIA.

We also have to think about delirium in the setting of acute confusional states in the emergency department. Emergency medicine has 30 years of research, showing that we really have not moved the ball at all on recognizing delirium. It occurs in anywhere from 8 to 10% of our patients, if you actually take the time to test them in research settings. ED staff are being pulled in multiple directions with lots of competing time priorities, only have a sensitivity of detecting delirium of about 35%.

This chart on the right is a study we had done at Washington University over a decade ago, where we actually had a research assistant do some formal cognitive assessment of patients, and then look at the chart and see if the ED nurses, the ED physicians, or the admitting physicians recognize the presence of delirium or dementia. And you can see that even with the ease of admission, for the admitting MDs, that 60% of these patients with abnormal mental status were documented, there's normal mental status on the inpatient

side. So delirium is something, yes, we need to recognize it. But we have to do some process improvement to get to that point in emergency medicine.

Dr. Galvin:
That's really a striking finding. I mean, I think that's really going to, you know, drive home some conversations with people as we start to think about how we're going to figure out is it ARIA? Or is it not? Is the symptom we're seeing related to the ARIA, or not?

So let's go back to our case then. So remember, it's a 71-year-old male, he had headache and gait abnormalities. We've talked about his medicines, but he's diagnosed with mild cognitive impairment due to AD. And he's on lecanemab, and this is the sixth that dose, so seven days ago. So should the duration of amyloid DMTs influence the clinical suspicion? So when does ARIA occur? Well, most ARIA events occur in the early phases of the amyloid beta targeted therapies. So the likelihood of ARIA tends to decrease the longer they've been treated. And so this really requires us to have an advanced - enhanced vigilance, right? So when someone's on drugs like lecanemab or aducanumab, or potentially in the future donanemab, what are we going to do to really monitor our patients carefully? We know from aducanumab, that ARIA is most likely to occur within the first 8 months of treatment. And in lecanemab, roughly the first 3.5, months over 14 weeks of treatment. There's also an investigational drug donanemab, and most ARIA occurred within 3 months. So during that time is really our greatest risk. That's what we really need to pay close attention to the signs and symptoms of this.

So again, let's think about our case. So we have now the signs and symptoms of ARIA, the typical timing of ARIA symptoms in relation to the initiation of amyloid beta therapy. So our next step then, regardless of the clinical setting, is to order appropriate imaging. Chris, what do you think?

Dr. Carpenter:
Yeah, I think that this needs to be on the radar of emergency medicine to be thinking about this constellation of events, the recent dosing of lecanemab, symptoms that are concerning for ARIA, and the opportunity to diagnose that with appropriate imaging and communication with radiology to make sure we have that communication loop.

Dr. Chiang:
I think it's very important that radiologists are given the history that the patients are actually on these disease-modifying therapies. And one of the challenges is patients don't always go to the same, you know, institution, the same facility for their imaging. And so the, you know, the radiologists may not have access to that history, of their medication history. And furthermore, the radiologists may not have access to their baseline scan.

Dr. Galvin:
So we think about this, you know, prior MRIs. So the baseline, you had three microhemorrhages, at the most recent, that's prior to the fifth dose, it was unchanged. So we have - we're able to go back and look at his records and see that we know there's three microhemorrhages. And that hadn't changed from his last MRI, which was just prior to his fifth dose.

So Gloria, tell us about what we can expect to find on imaging?

Dr. Chiang:
Sure. So we actually grade the severity of ARIA using the sort of mild, moderate, severe grading scale. And as we talked about earlier, there are two forms of ARIA, there's ARIA-E and ARIA-H.

So this slide is showing you what ARIA-E looks like, or the edematous form. And so for example, in the first image, the circles delineating this T2 hyperintensity on a flare sequence in the left superior frontal cortex involving subcortical white matter. So this is essentially vasogenic edema in the left frontal lobe. Because it's only one location and it's small, it's less than 5 centimeters, it's considered mild.

For the image in the center, again, this is on a flare sequence, you have T2 hyperintensity that's within the sulci at the right temporooccipital junction. And so this is basically fluid or an effusion within the sulci. In this case, because it's a larger area, even though it's one location, it's considered moderate. If they were small areas of effusion, or edema but there's more than one location, it would also be considered moderate.

And in the third image on the right, you can see there's actually two areas of T2 hyperintensity within the brain, one in the right frontal lobe and one in the right parietal lobe. So this patient has two areas, so more than one location involved, and they're both large. And so because of that, this would be classified as severe ARIA-E.

Dr. Galvin:
Gloria, if I could ask you, particularly, you know, for the – if the audience might be thinking this is that, you know, we see older adults with images, they often have white spots, right? They also have, you know, bright spots. And I think we can see a little bit on the - in the

severe case in the left hemisphere, you know, some of those white spots that we might typically think about as being ischemic white matter changes. But this is different. This has really a different sort of appearance, this sort of tracking through the white matter, right?

Dr. Chiang:
Yeah.

Dr. Galvin:
Like a clinical pearl for the audience, how would you help them if they're looking at this?

Dr. Chiang:
Yeah, I mean, that's a great point. I think one really important thing for both ARIA-E and ARIA-H is that we'll have a baseline MRI. So absolutely, people who are older, they tend to have these sort of white spots, or white matter hyperintensities, as we call it. Similar to what we're seeing the left hemisphere here, they're often more punctate. As they become more advanced, they might become more confluent, but they tend to be more central or sort of a little patch here, a little patch there, versus the vasogenic edema that we're seeing with ARIA is really confluent. So like, for example, in the severe case, you can see that right frontal lobe, it's this large area of confluence rather than sort of the punctate or the patchy stuff that we see with white matter hyperintensities related to age or cerebrovascular disease.

Dr. Galvin:
Okay, great. I think that's really going to help clinicians in the audience when they're thinking about how they're looking at these scans. What about ARIA-H?

Dr. Chiang:
Right. And so, this is our grading scale again applied to ARIA-H, which is more of the hemorrhagic form. And this is going to be seen on either a gradient echo MR sequence or susceptibility weighted MR sequence. And so, for example, in the first image, you can see the circle is delineating this area of dark signal. So dark signal within the sulci compatible with superficial siderosis. And the arrows are pointing to these punctate foci of dark signal, which are the small areas of microhemorrhage. And so because this patient has less than four microhemorrhages, this is considered mild. And this patient also has just one focal area of superficial siderosis. So given both of those, it's still considered the mild category of ARIA-H.

The middle image you can see there's the circle and an arrow, so both frontal lobes have the superficial siderosis. So again, this hemosiderin that's within the sulci of the frontal lobes. So because it's two areas, it’s now considered moderate. It's not shown in this image, but the patient had between five and nine microhemorrhages, so more microhemorrhages than would be classified as mild, this would also be considered moderate.

In the third image on the right, you can see the circle is describing a lot of these punctate foci of microhemorrhages. And in this case, the patient actually had more than ten microhemorrhages. Because of that they're classified as severe ARIA-H. If the patient also had areas of superficial siderosis that were more than two areas, that would also be classified as severe. So this is sort of how were classifying ARIA-E and ARIA-H to hopefully guide management of these patients.

Dr. Galvin:
Chris, in the acute care setting, you know, we really need to use an MRI to see a lot of these effects. Often when people come in through the acute care setting, because MRI takes so much longer, outside of University Hospital, the choice may be to do a CAT scan. Is this going to change the way ED physicians may be thinking about ordering imaging for their patients?

Dr. Carpenter:
I don't know, Jim, I think that the MRI is certainly a rate limiting step for the academic emergency department that has access to MRI 24/7. In the rural setting, many hospitals don't have MRI at all, or certainly not during nighttime hours in which you have to package the patient up, transport them to the center that has the MRI, get that center to accept the patient. And in some of these rural settings, that can take out the only EMS unit that the county has. So I think we'd have to see a lot more data. What's the pretest probability of this in this population? What is the number needed to test to identify this pathology? And there's so many other conditions that present with some of these symptoms that are going to be much more common. I think we need to see a lot more data before I can say how it's going to shape and change how emergency medicine is delivered.

Another situation that comes up in the emergency department frequently with MRI orders is patients that cannot get the MRI for whatever reason, they've got some hardware. Sometimes it's that MRI is so backed up if they don't see some conditions as a time-dependent emergency and this needs to be prioritized to tomorrow or next week. How would you suggest that ED providers manage those situations where we suspect ARIA but can't obtain the MRI imaging?

Dr. Chiang:
I think that's a very challenging question. And so basically, these microhemorrhages are punctate as you can see on the MRI, so we're not going to see them on a CT scan. And similarly with the superficial siderosis, we're not going to see it on a CT scan, because CT is not sensitive enough for those who are small areas of hemorrhage. You could potentially see the edema on CT. So in terms of you know, if you want sort of a quick screen, at least for the ARIA-E vasogenic edema, CT might be useful. But again, for ARIA-H, you really need MRI to be able to see these findings.

Dr. Carpenter:
Those are conversations the emergency physician should have with radiology when it's a queuing problem, that we don't think this is important enough to get the MRI right now?

Dr. Chiang:
Yeah, I think that all the stakeholders have to be around the table and kind of discuss what to do in those instances. Right? So even patients that have pacemakers, you know, we have protocols in place, you know, with electrophysiology to try to monitor them safely while they're getting an MRI, for example. Or, you know, treating this really as urgently as some of the other ED patients in terms of getting their MRI, because it could change whether or not you need to stop the therapy, right? Even though it's rare, vasogenic edema does cause mass effect, and it could cause herniation. And these are the significant things that we need to think about with these patients.

Dr. Carpenter:
Thank you.

Dr. Galvin:
So you know, are the findings resembling ARIA on MRI enough to confirm that the patient is actually experiencing ARIA?

Dr. Chiang:
So without that history, again, if we saw a couple of microhemorrhages, we may not think much of it. Even if we saw some superficial siderosis, a lot of older patients have, you know, concomitant amyloid angiopathy. If the patients stay symptomatically wouldn't think that much of it. But given the history of one of these DMTs, that would alert us to then be more cognizant of these findings and how these findings could actually change management. So I think having that history of the fact that they're on these DMTs is really important.

Dr. Galvin:
So let's go back to our case now. Remember, 71-year-old male, MCI due to AD, got the sixth dose of lecanemab, has symptoms. So we say he has symptoms of ARIA, the timing is typical for this, considering the relationship to the initiation of therapy. So here's their MRI results. And again, you can see the mild edema, but we also see these mild by microhemorrhages so 1, 2, 3, 4, 5. Yes, I can count. So we have five microhemorrhages, we have mild edema. So by definition, this would give us moderate ARIA-H and mild ARIA-E. Right? So clear evidence that ARIA is present in this individual. They have symptoms of ARIA, the timing is right. The diagnosis is right, the medication is right. So it's all fitting together. So what are we going to do? Right?

So I think it's important to think about how we address this. What's the impact of ARIA on DMT? And does this person need to stop their medicines? Now in the clinical trials, 94% of patients with ARIA were managed without discontinuation. That's an important factor to remember, but again, you need to look at the patient right in front of you. So ARIA is on the MRI, the first thing you have to ask is the patient's symptomatic or asymptomatic.

If they're asymptomatic, then you look at the MRI. If it's mild on the MRI and they're asymptomatic, you could continue treatment, and then just do monthly MRIs to watch for any further changes. Okay? If they're asymptomatic but they have moderate or severe changes on the MRI, the recommendation is to suspend the treatment, do monthly MRIs, watch for the symptoms to resolve and for the MRI to show some resolution or stabilization. After that, then you can discuss resuming therapy.

Now if the patient is symptomatic, like our guy - case history here, so first, do they have mild symptoms, or just mild ARIA-E on MRI? Based on clinical judgment, you could choose to continue treatment and then have monthly MRIs for monitoring and watching changes. However, if they have moderate or severe ARIA of any type, or at least mild ARIA-H, then the recommendation is to suspend treatment, do monthly MRIs, wait for the symptoms to resolve, make sure the MRI is showing resolution or stabilization, then you can consider resuming treatment. Okay?

So we have an algorithm that allows us to think about it for this particular case. So if you remember, we have a symptomatic person, right? They have ARIA-H and ARIA-E. Right? They have mild ARIA-E, moderate ARIA-H because of the five microhemorrhages, so we'd be in this pathway based on this case report.

Dr. Carpenter:
This is really foreground now as, Jim, for emergency medicine, I think it's going to be important for each healthcare team to work with their prescribers to - between emergency medicine, neurology, primary care to make sure that that protocol is available in the scenario arises in the ED, either by telephone communication or something on the electronic medical record.

Dr. Galvin:
Right. I think as we develop and fine tune all these algorithms, they're really going to help us, particularly in those acute settings, where we have to make snap decisions on what's the best thing to do for that patient that's right in front of us.

So based on everything we hear the plan would be for this patient then to go out, outpatient follow-up with their neurologist, and that the schedule for when the monoclonal antibody could be restarted and/or MRI monitoring could be scheduled and adjusted as needed. Right? So the fact is now we can work as a team. You know, the ED can communicate with radiology, communicate with a neurologist, and we can have a plan that's the best for this patient, given all the circumstances and data that we have available to us.

So what if this person had severe ARIA? Right? So now let's just change the MRI. And now we have multiple, multiple treatment-emergent microhemorrhages. There's more than ten here. You count all little black dots, right? So really meets the criteria for severe ARIA-H. Gloria, tell us where we're going with this, what's the - what are we learning from this?

Dr. Chiang:
Yeah, so in terms of prompts for DMT discontinuation, on the radiological side, any macrohemorrhage that we see. So microhemorrhages are typically less than a centimeter. But if you have a macrohemorrhage that's larger, you would consider stopping the medication. Again, if you have more than one area of superficial siderosis, you're no longer considered mild ARIA-H, so you would consider stopping the DMT. And in this case, we described that there was more than ten microhemorrhages. So again, this would be something that you would consider for stopping the therapy.

On the clinical side, you would consider stopping the therapy if there are more than two episodes of ARIA, or if you have severe symptoms, or development of any sort of medical condition that requires anticoagulation. Because as we mentioned, with ARIA-H, you already have hemorrhage within the brain. And so, giving someone like that who's already prone to hemorrhage anticoagulation could be dangerous.

Dr. Galvin:
Right. Yeah, and again, you have always have to think about the patient that's right in front of you and what's happening. So algorithms are great, prompts are great. But you also have to look at the person in front of you and, you know, take that all into consideration.

So Chris, this - now persons in the ED, you have all this information in front of you, what's next?

Dr. Carpenter:
Well, I think that this is where the team-based approach to care really comes into play. We have to lean upon our neurologist on the inpatient side, preferably a vascular neurologist, not every community hospital is going to have access to a vascular neurologist. Sometimes it's going to be transferred to tertiary care medical center. Perhaps some committee hospitals are very long distances, like a flight away from the tertiary care center, using telemedicine to get access to those folks, and having criteria in place at your hospital for when you admit this patient. And for severe ARIA, I can't imagine sending very many of these folks, if any, home. But do they go to the ward? Or do they go to the hospital service of neurology consult, to the neurology service, do they go to the neuro ICU? I think each hospital is going to come up with their own protocols for those decisions.

There's some therapies that we should be thinking about in the emergency department as well, again, I think, in conjunction with our neurology consultants. One is high-dose glucocorticoids, methylprednisolone at 1 gram per day for 5 days, and then a prednisone taper over weeks or months. And certainly, if the patient is seizing in front of us, or an EEG is obtained and there's epileptiform activity, we need to be thinking about anticonvulsants. And again, I think doing that in conjunction with our neurologist.

Dr. Galvin:
Alright, so this module is also summarized in a downloadable interactive infographic so you can access the information quickly, on your own time. You can find the link on the program landing page. Make sure you check out the closing module of the activity, where we really have a multispecialty discussion of the collaborative management of ARIA. So in that module, we're going to have a discussion of the entire team and really try to think about how all this comes to play so that we can have a collaborative discussion and think about team-based approach to caring for the patients.

Thank you, Gloria and Chris. I think this was a really exciting and interesting module and activity.

Dr. Carpenter:

Thank you.

Dr. Chiang:
Thanks, Jim.

Announcer:
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