Acute Disseminated Encephalomyelitis

Diagnosis and Treatment Guidelines

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Krissy Dilger: [00:00:00] Hello and welcome to the SRNA "Ask the Expert" podcast series. This podcast is entitled “Acute Disseminated Encephalomyelitis: Diagnosis and Treatment Guidelines.”

[00:00:12] My name is Krissy Dilger, and I will be moderating this podcast. SRNA is a non-profit focused on support, education, and research of rare neuroimmune disorders. You can learn more about us on our website at wearesrna.org.

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[00:01:37] Horizon is focused on the discovery, development, and commercialization of medicines that address critical needs for people impacted by rare, autoimmune, and severe inflammatory diseases. They apply scientific expertise and courage to bring clinically meaningful therapies to patients. Horizon believes science and compassion must work together to transform lives.

[00:02:03] For today’s podcast we are pleased to be joined by Dr. Farrah Mateen and Dr. Cindy Wang. Farrah J. Mateen, MD, PhD is Associate Professor of Harvard Medical School at the Massachusetts General Hospital. Dr. Mateen is originally from Saskatchewan, Canada where she received her medical degree in 2005. She pursued adult neurology training at the Mayo Clinic in Minnesota and a Fellowship in Medical Ethics at Harvard University in 2008. Dr. Mateen's clinical and research fellowship training was in Neuroimmunology & Neurological Infections at the Johns Hopkins Hospital, supported by the American Brain Foundation. Dr. Mateen completed her doctoral studies in International Health Epidemiology at the Johns Hopkins University in 2014 as a Sommer Scholar.

[00:02:56] Her clinical practice at Mass General Hospital is focused on neuroimmunology, including MS, ADEM, NMO, and related disorders. Dr. Mateen was the Chair of the American Academy of Neurology's Global Health Section and Ethics Section and is past chair of the International Outreach Committee of the

American Neurological Association. She has worked with the UN High Commissioner for Refugees, World Health Organization, Polio Eradication Initiative, and several NGOs across the countries of various income levels. She has published 200 academic manuscripts to advance neurological disease research and clinical care to date.

[00:03:41] Dr. Cynthia Wang received her medical degree from University of Texas Southwestern Medical Center in Dallas, Texas and completed a pediatrics and pediatric neurology residency at Mott Children's Hospital, University of Michigan Health System in Ann Arbor, Michigan. Dr. Wang completed her James T. Lubin Fellowship under the mentorship of Dr. Benjamin Greenberg at The University of Texas Southwestern and Children's Health. Her research study was a prospective, longitudinal study on acute disseminated encephalomyelitis to identify the clinical characteristics, treatment methods, and follow-up interventions that are associated with better and worse patient-centered outcomes.

[00:04:27] Welcome and thank you for joining us today. Our first question is can you begin by giving an overview of what acute disseminated encephalomyelitis, or ADEM, is? Dr. Wang, do you want to start us off?

Dr. Cindy Wang: [00:04:43] Sure. Yeah. And thank you, Krissy, and GG, and the SRNA for having me it's always a pleasure to talk to your organization.

[00:04:50] So yeah, I usually just like to break down the name of the condition, which seems very intimidating, but I think when you just view it as its individual parts it becomes a lot more understandable. So, acute referring to a fairly abrupt or sudden onset of symptoms, disseminating, referring to widespread or multifocal symptoms or multi-focal brain lesions, and then encephalomyelitis refers to inflammation of the brain and spinal cord.

[00:05:16] The brain is pretty, you know, pretty much of a requisite to making the diagnosis and the spinal cord can be involved but doesn't always have to be. And yeah, it's a syndrome, meaning that sometimes, you know, we can find an exact cause that we know a bit more about the reason it happens, but other times we may not understand, you know, what exactly causes it.

Krissy Dilger: [00:05:37] Okay, great. Thank you. Our next question is for Dr. Mateen, what are the signs and symptoms of ADEM in the acute stage?

Dr. Farrah Mateen: [00:05:45] Great and, first of all, thank you for having me. It's really a pleasure to be here as well. So, the signs and symptoms of ADEM in the acute stage might be different depending on the patient. And it's really dependent on where the lesion is in the brain and or the spinal cord. So, one of the hallmarks of ADEM is something that's called encephalopathy, at least that's part of the criteria for kids. And that means that there's a alteration in the level of awareness. But some people may experience a weakness, for example, changes in sensation.

[00:06:16] And these tend to be a rapid onset within a matter of hours or even days. And sometimes a seizure is present, but this is usually something that's a noticeable change in function. So, it's not minute to minute, it's a new onset deficit that didn't occur before. Usually, it's weakness or changes in awareness.

Krissy Dilger: [00:06:36] Okay, great. Thank you. Our next question is what is the cause of ADEM, Dr. Wang?

Dr. Cindy Wang: [00:06:42] Yeah, and I think many very smart researchers and investigators have tried to, you know, answer this question, not only for ADEM, for other myelinating autoimmune diseases. And I don't know if we understand it and it may be difficult to define one cause because ADEM is probably, you know, consists of many different diseases that all can appear clinically the same or radiologically have similarities.

[00:07:07] But I think at the basis, it's thought to be some sort of immune dysregulation that happens. And usually there is some sort of a trigger within the environment, whether that's an infection, it's most often infection. There may be other things that we aren't sure of exactly or we don't identify a trigger. And then perhaps a genetically vulnerable person who may have, for whatever reason, a higher risk of having, you know, a dysregulated immune response in response to that trigger.

[00:07:37] So it's considered a post-infectious condition. So, not necessarily something directly related to an infectious insult, but something that happens after the immune system has encountered, you know, and oftentimes fought off an infection. And then in terms of mechanisms, there's been speculations that maybe some organisms have some similarities, so the appearance of constituents of the brain and the spinal cord, specifically myelin, which is the insulating coding of nerves in parts of the brain. And yeah, because of this sort of misdirection of the immune response, you get our own body's tissues targeted instead of, you know, perhaps a microorganism.

Krissy Dilger: [00:08:17] Okay, great. Thank you. The next question is what are the demographics for people who have ADEM? For example, is it more likely to occur in children, Dr. Mateen?

Dr. Cindy Wang: [00:08:29] Yep. And I think Dr. Wang just answered the hardest question of all. So, this one is a little bit more straight forward. So, the average age of somebody presenting with ADEM is usually in late childhood, early adulthood. So, somewhere between the ages of about 10 and 30 years old. Having said that ADEM can present in infancy rarely and it can also present later in life. So, in older adults, you can have an ADEM presentation, but I would mention that those are relatively rare. So, we're used to seeing this condition usually equally in women and men or girls and boys. It's approximately equal or at least similar in early adulthood and children.

[00:09:11] And we've done some work on ADEM epidemiology in different parts of the world. And it actually looks fairly similar, no matter what country you're in. So, even though triggers might be different and causes, as mentioned, are not always clear. The pattern of ADEM tends to be similar no matter where you live.

Krissy Dilger: [00:09:29] Okay, thank you. Our next question is how is ADEM diagnosed? For example, what are the diagnostic tests used, the clinical characteristics, et cetera?

Dr. Cindy Wang: [00:09:41] Yeah, so, and yeah, that was definitely a great point by Dr. Mateen, that, you know, the demographics can vary, yeah. In children I see they're typically a bit younger, more maybe around the early school age, but yeah, I agree that it's really, not you know, it doesn't seem to favor women like some other conditions like multiple sclerosis and NMO. So, I think that's one of the things that kind of distinguishes it from the other conditions.

[00:10:06] And then, like many of these conditions, we similarly use the same tools to explore, you know, what they could be, you know, really starting at the core, which is getting a good story. You know, many of these conditions, we hear symptoms evolving over typically days to maybe one, two weeks. A progressive worsening of that encephalopathy Dr. Mateen referred to, which in children can be variable from irritability to maybe just tiredness versus, you know, very significant things like seizures and almost a comatose state.

[00:10:36] But yeah, that history, I think really clinches, you know, this condition versus other things that may progress at a faster or slower pace. And then we look for other things, primarily neuroimaging at the brain and the spinal cord, if pertinent, to look for a pattern that would be consistent with ADEM, which are usually large or asymmetric lesions in the brain with indistinct margins that do look a bit different for multiple sclerosis and other demyelinating conditions.

[00:11:04] We often will survey or explore what the spinal fluid shows to evaluate if it's a consistent pattern, which may show signs of too many immune cells, perhaps elevated protein, other markers. But a lot of these tests are also to help exclude mimics of ADEM, which can be infection, sometimes cancers, and other metabolic conditions.

[00:11:27] Yeah. So, it's primarily a clinical and radiological diagnosis. Other things like spinal fluid and blood tests, looking for specific antibodies that can be associated with ADEM are important. Yeah. And then for children, like Dr. Mateen mentioned, encephalopathy is a big one. I think it's not necessarily involved in the adult criteria, but just, yeah, some sort of alteration in awareness or level of consciousness, which makes sense with what we see in the brain, when many parts of the brain are involved.

Krissy Dilger: [00:11:55] Great, thank you for that explanation. And our next question is related to that. Are there any differences with how pediatric patients are diagnosed versus adults, Dr. Mateen?

Dr. Farrah Mateen: [00:12:08] So, I guess in some ways no, I would say is that the general answer, but in children, there are specified criteria and they come from the international pediatric multiple sclerosis study group, who's interested particularly in figuring out who has ADEM, who has MS, and who has other, a different condition. And so the pediatric criteria are, you know, validated and understood best in children. In adults, because ADEM is less common in adults, there's always a little bit more of a, I guess, some scrutiny, 'Is this multiple sclerosis, is this neuromyelitis optica?' So, the pediatric criteria are applied to adults.

[00:12:50] We're looking at the imaging really carefully, looking for lesions that are on the larger side, usually more than two centimeters in diameter. But, in general, all of the same principles apply. And under, not that we're able and would want to do this, but under the microscope, you know, it would look the same, no matter what age you are because ADEM actually has that, it's doing a certain thing in the brain. It's just, we can't always see it. We have to sort of work around it with MRI and blood tests, et cetera.

Krissy Dilger: [00:13:19] Okay, great. Thank you. Our next question is how is ADEM differentiated from anti-NMDA receptor encephalitis, Dr. Wang?

Dr. Cindy Wang: [00:13:28] Yeah. It's a great question because I think in how a child or adult may present, there can definitely be a lot of overlapping clinical features such as changes in behavior, or mood, or cognition thinking, memory, so forth. The, the good thing is that now we're getting better at, you know, having specific blood tests for anti-NMDA receptor encephalitis.

[00:13:50] There's a specific test that can be sent with the spinal fluid and blood that is really quite a good test. That's both sensitive and specific. So, you know, meaning that if you get a positive test, you can be pretty sure that that's the condition. And then for ADEM, there's not a single test. So, we've learned a lot in the last few years about MOGAD or anti-MOG related demyelinating syndromes, probably one of the most common syndromes of which is ADEM.

[00:14:16] So, yeah. I think, if you can find one of these specific markers, whether it's MOG or NMDA, that does give you a fairly confident, you know, diagnosis. And then if you do not find these antibodies, there are still, I think clinical differences. ADEM affects the white matter. You know, it's primarily characterized as a demyelinating condition. NMDA and other autoimmune encephalitities usually affect the neurons themselves and, as a result, the MRIs may actually look pretty normal. But typically those conditions affect the function of the neurons and thereby lead to other things like more significant behavioral changes or seizures. So, usually those are the biggest clues that separate the two syndromes.

Krissy Dilger: [00:15:00] Okay, great. Thank you. And you mentioned the MOG antibodies. So, our next question actually is what is the relationship between MOG antibodies and ADEM? If there are MOG antibodies detected, does that exclude an ADEM diagnosis, Dr. Mateen?

Dr. Farrah Mateen: [00:15:17] Yeah. So, I think of these as overlapping situations. So, ADEM may or may not have MOG antibody present. So, ADEM is a clinical syndrome. It describes the, you know, the experience of the patient. And a fraction of patients with ADEM, particularly children, may have that test, the MOG antibody present, but you can have ADEM and not have a MOG antibody. And that's the most common situation.

[00:15:47] Similarly, you can have a MOG antibody and not have ADEM. So, MOG antibody is a blood test, and we have patients who have MOG antibody disease and some of those folks have ADEM, but a lot of them don't have ADEM. They have optic neuritis or spinal cord changes. So, this is sort of like an overlap between a test and a syndrome.

[00:16:06] And there is a fraction of folks who have MOG antibody and ADEM, but they're not lock and key. You don't have to have one to have the other.

Krissy Dilger: [00:16:14] Okay, thank you. We did just get a question in from the community, and I know MS was addressed a little bit earlier, but this person wants to know is ADEM a precursor to MS, Dr. Wang?

Dr. Cindy Wang: [00:16:27] Yeah, that's a wonderful question. I think one of the most satisfying things I can tell a family and a child is that, you know, well, typically if everything is consistent with ADEM, there's a very high chance it's going to be a monophasic or a one-time illness, that it's not likely to happen again.

[00:16:42] There are a few exceptions to that. Namely, if we do identify AMOG antibodies, you know, with the initial presentation, there are known to be cases of anti-MOG disease that do relapse, and it may come back as ADEM or it may come back as something else such as optic neuritis, inflammation of the optic nerves, or transverse myelitis, or sometimes just called myelitis, which is inflammation in the spinal cord.

[00:17:06] And yeah, I think it's really important to be able to tell a family this at the beginning because usually even at the very onset you can give the families a pretty good sense of, you know, is this look more like multiple sclerosis or if it's ADEM? And some of that comes from the demographic features, some comes from the spinal fluid in the MOG testing.

[00:17:27] But yeah, I would say if it is not appearing to be atypical ADEM, then it's usually, if not, almost always the case, not going to lead to ADEM, which I find to be reassuring, you know, as a physician and a nice thing to tell families.

Dr. Farrah Mateen: [00:17:44] So, what are the acute treatments used for ADEM and what's the timeframe over which you could receive them? And so, this, to be honest, there's not one right answer.

[00:17:56] So, this is kind of where that art of medicine comes in as well as the science. So, as everybody knows on the call, ADEM is rare. I guess we didn't talk about that, but it's an uncommon presentation. It's more common in kids, but we're still talking about one in several hundred thousand to one in a million people, depending on the age.

[00:18:15] So, we don't have a lot of like randomized controlled trials and hundreds of people enrolled to tell us what the right answer is in everybody. And we often look at the level of impact of the disease on the patient

before we make a decision. But to really give you like the, kind of the laundry list of the acute treatments, the most, so if a patient's doing really well, we won't do anything, but if a patient needs something, steroids is the first pass we often get.

[00:18:42] When we looked at a study, we looked at four different hospitals and what everybody did. Adults are more likely to get treated I think a little more aggressively than kids, where I think people are careful to really make sure they need that immunosuppression, but steroids, prednisone, or methylprednisolone, as the most common, usually it's given in an IV daily for about three days, five days.

[00:19:07] And the hope is that that is sufficient to sort of stop the immune response. If that is either not fully successful or if we think we can get more benefit from continuing, you can either keep going with that, you can do a pill-based taper, which means to take a little bit less every day to just get the immune system sort of treated, but to come off of that kind of blast on the immune system.

[00:19:31] Other things that we use are things called IVIG, or intravenous immunoglobulin, and that's really like a blood product to try and kind of flush out the cause of ADEM from the bloodstream. And some people have even tried plasma exchange, which is something that you need a line into your vein. And they basically replace part of the blood with donor blood or treated blood, and that's meant to get rid of any of the causes of ADEM, but there's a lot of stuff out there and it's kind of a step-by-step approach.

Krissy Dilger: [00:20:01] Okay, thank you. And then kind of going off of that, can you explain why you might use one treatment over another or why some people might receive multiple treatments and others only receive one, Dr. Wang?

Dr. Cindy Wang: [00:20:16] Yeah, and I really echo what Dr. Mateen said, that, you know, high dose steroids is our first-line treatment. Primarily because it's really accessible. We can get it started quickly. It usually doesn't hurt, you know, other conditions that could be in the differential.

[00:20:31] And yeah, it's accessible and it works pretty fast to decrease inflammation and preventing any insignificant injury. I think it differs a lot by institution. I come from an institution where, you know, my predecessors were very opinionated about starting plasma exchange early, specifically for children and adolescents who had very significant, severe symptoms at onset.

[00:20:52] So, as our institution operates, many of the times we might start using medications simultaneously, so starting steroids, but also very quickly escalating to plasma exchange. And that's because we think that, you know, maybe using two treatments earlier on might preserve, you know some tissue.

[00:21:11] And so, the significant cases might be if somebody has really significant myelitis, in which they can't move their arms or legs. If they have really severe bilateral optic neuritis and they cannot even, you know, see movement or light, then that'd be a situation where we just want to treat a little bit more aggressively.

[00:21:29] But I think many institutions might do a step wise or a stage approach with first doing IV steroids and then if, you know, symptoms are not remitting, then maybe considering plasma exchange. Like Dr. Mateen mentioned, you do have to, in at least children, place a wide catheter typically into the neck and, you know, that comes with risks of bleeding and infections.

[00:21:48] So, we generally don't take it lightly and many institutions are even more reluctant to use that approach. So, IVIG, or intravenous globulin, I feel like in many pediatric centers is sort of the second line treatment.

[00:22:01] But yeah, there's not any, you know, one, you know, ideal or perfect approach and that's where the art of, you know, taking care of these individuals come in. And it's difficult because, you know, we don't, we have sort of expert opinion and consensus among people who treat these conditions. But we don't have like a specific guideline that says, you know, if 'A,' do this, which, yeah, can be both challenging, but also a bit freeing in, you know, using your discretion about how aggressively to treat someone.

Krissy Dilger: [00:22:32] Okay, thank you. Our next question is can ADEM recur, Dr. Mateen?

Dr. Farrah Mateen: [00:22:40] Yeah. And that's definitely a controversy, a controversial question. So, for the most part, no. The general thinking is that ADEM is monophasic, which means that it is a one-time, really significant impact on the nervous system.

[00:22:54] Having said that, there is a literature that says about 2% of ADEM, people who've experienced ADEM have ADEM again, but that's a rare situation for a rare disease. So, can it happen? I guess, in theory, yes. Is it likely to happen? Really, it's very, very unlikely that it will happen. It's been described in like single cases. But for the most part, ADEM, I think, should be considered as a monophasic condition.

Krissy Dilger: [00:23:21] Okay, thank you. My next question is, can you have another rare neuroimmune disorder in addition to ADEM, such as transverse myelitis or MOG antibody disease, Dr. Wang?

Dr. Cindy Wang: [00:23:33] Yeah, and I mean, it's, it's a good question. I think when it comes to terminology with these conditions, we're still learning a lot. And, you know, sometimes I think of them as being like, you know, a subset of one of the others or overlapping. So, it's really hard to say, you know, ADEM includes myelitis. So, you can have concurrent brain and spinal cord involvement and thus have, you know, a transverse myelitis spinal cord inflammation, in addition to the brain inflammation.

[00:24:01] And then the question of MOG is more like, you know, targeted at, you know, do we know a specific reason or, you know, for the things that we can test, can we find, you know, a cause or at least something to say that it just was caused by an infection and MOG is one of those conditions that we can test for.

[00:24:20] I think the beauty of being able to do that, as was done with neuromyelitis optica spectrum disorders, is that gives us sort of a platform to really start learning about, you know, the mechanism of a specific disease. So, yeah, I would say you can have more than one part of the brain involved. You can have the brain, you can have the optic nerves, you can have the spinal cord, and that can come either, you know, sequentially, you know, as a relapse or at the same time. And it kind of depends on the etiology, which MOG is one of them. And I think a lot of the literature suggests that MOG often does just strike once, you know, one like immune exacerbation, so to speak.

[00:25:00] But, in some cases, maybe as high as a third to half the time, if we, you know, follow a person long enough, it might come back in a different part of the immune system. But we're still kind of premature in how we predict whether one person will just have it once or if they'll have a relapse.

Krissy Dilger: [00:25:15] Okay, thank you. Our next question is what does the recovery process involve following an ADEM diagnosis? Do people typically fully recover, or can there be lasting damage, Dr. Mateen?

Dr. Farrah Mateen: [00:25:29] So, everybody's different, of course. I have seen a range of different possibilities. Some people do seem to recover fully. They go back to, you know, the original life. But it often isn't right away. It takes, you know, weeks, even months for a lot of people to sort of recover from the extent of how their brain had that major impact.

[00:25:54] And also, it's not just the disease itself, but the, you know, the treatment, and the hospitalization for most patients, and just kind of the surprise of having that condition. And it does take time, even in the best-case scenario. And then there are some scenarios, to be honest, where the lesion remains, and the impact is still there. And so, once the brain has had a lesion or several lesions, usually the damage can be lasting, and it may not be immediately apparent.

[00:26:21] I would mention some really interesting work done actually from Europe that looks at children and how they do in school after ADEM. And some kids still have difficulty doing really well in school or paying attention and fatigue has been reported. And so, some of the challenges afterwards are desegregating what is from ADEM and what is not from ADEM. But a range is possible from complete recovery to, you know, there is a tiny group of people with ADEM who die of ADEM, and it's a really small number, but I just mentioned there's a whole range of things that can happen.

[00:26:55] And thankfully, people generally do well, but it really depends on how, you know, how much of the lesions are impacting their brain and spinal cord and how well they respond to the treatments we provide.

Krissy Dilger: [00:27:07] Okay, thank you. Our next question, is there a difference in prognosis for children who are diagnosed with ADEM versus adults, Dr. Wang?

Dr. Cindy Wang: [00:27:17] Yeah. You know, I definitely see a lot more children with ADEM than adults. But I think the literature suggests that adults who have ADEM may have, you know, a more significant protracted illness and perhaps less complete recovery. You know, generally we think maybe 80 to 90% of children, more or less, recovered to their pre-ADEM baseline. I think that that could be different in adults.

[00:27:39] And yeah, I think it's a really good point that, you know, in many of these conditions, you know, how we study them, determine what we consider a good prognosis. If we're just looking at, if somebody can walk and if they can, you know, communicate, that may be a really low bar to set.

[00:27:54] If we do more, you know, thorough neuropsychological evaluation looking at detail, at processing speed, you know, visual motor integration, executive functioning, it is often that we do identify some deficits and, yeah, I think this will get to one of the follow-up questions. With children, I think it's a dynamic, you know, it's a disease applied to a dynamic kind of individual where there's already, you know, there's development happening. So, depending on what age somebody gets this or has this condition, it may, you know, more significantly or less significantly affect their development and their recovery.

[00:28:32] So, yeah, I think probably, for the most part, children do well, but there certainly are those cases where it's, you know, a very significant sometimes fatal illness or there are lifelong deficits, cognitive or physical.

Krissy Dilger: [00:28:43] Okay, thank you. Our next question is about rehabilitation. Dr. Mateen, is rehabilitation recommended following an ADEM diagnosis? And how long should the rehabilitation process last?

Dr. Farrah Mateen: [00:28:57] Yeah, and that's a very personalized story. So, we've been kind of mentioning how ADEM is different in different people. And so, and just, you know, to try and do justice to the whole field of rehabilitation, so basically there's, you know, there's occupational therapy, there's physical therapy, there's speech therapy, and there's all sorts of ways to interact. And I guess rehabilitation even more broadly speaking can be like getting back to, you know, exercise and more complex things too.

[00:29:30] So, if there are lasting problems from ADEM, it makes perfect sense to seek out these really excellent resources and generally they start where their therapists and the physicians are doing things actively with

the person. And over time, to the extent possible, the patient, him or herself, with family and other supports tries to take on some of the tasks, him or herself.

[00:29:59] But, you know, we've certainly engaged all sorts of experts. So, from speech therapy, to people who help with swallowing, to physical therapy, we depend on our physical therapists a lot. And one thing just to add to like, in terms of the duration of rehabilitation, this usually, I could, had kind of alluded to, really takes months.

[00:30:17] So, sometimes it's coming out of the hospital where they're really the first thing, you know, encounter where you see rehabilitation alone. And then it's always good to sort of check in with your neurologist or your physician. And sometimes we reconsult therapies over the course of a disease just to make sure that progress is not lost and that, you know, we're still doing all the right things.

[00:30:39] So, sometimes that process is it starts and then you take it on and then it stops and then you re-engage. So, it's kind of hard to answer one amount of time, but generally I found that collaboration very useful.

Krissy Dilger: [00:30:52] Great. Thank you. Our next question is kind of about after that acute phase, as the patient is discharged, kind of what they should be aware of on an ongoing basis.

[00:31:04] So, what type of doctors should an ADEM patient see? And if someone doesn't have major problems or concerns, do they still need periodic checkups with a neurologist or any other specialists from time to time, Dr. Wang?

Dr. Cindy Wang: [00:31:19] Yeah. Well, I think you've invited two neurologists, so we're a bit biased about that, but yeah, generally in the hospital and outpatient, it's primarily a neurologist because this has been considered something, you know, we take care of and treat.

[00:31:33] I think just as important, particularly if a person has a fairly incomplete recovery is a physical medicine and rehabilitation doctor, just because they are often the most savvy in how do we, you know, advocate for the most therapies, the appropriate equipment, when it comes to persistent motor deficits.

[00:31:54] There can be some people who have bowel or bladder issues following ADEM, particularly if it affects the spinal cord and a urologist may be helpful. And then, at our clinic, because we're really concerned about kind of the neurocognitive development of our patient population, our neuropsychologist does extensive interviews and testing with the child and engages with the family, just to make sure we're providing the appropriate amount of support so that, you know, when they do return to school or work, whatever it may be, that they're in a good position to succeed and not get frustrated by too high of a demand for how they're doing.

[00:32:29] So. Yeah. I think a neurologist and, you know, it just really depends, I guess, also by institution. Where I trained, we didn't necessarily follow these patients many years. But I think here, at UT Southwestern, generally we see, you know, patients at least three to five years just to make sure everything's okay.

Krissy Dilger: [00:32:48] Okay, great. Thank you. Our next question came from the community. Do you find that some people with ADEM progressively get weaker over the course of years? And if so, will it continue to get worse? Is there anything that can be done to stop or slow down worsening symptoms as a person ages, Dr. Mateen?

Dr. Farrah Mateen: [00:33:09] So I guess, to provide a counterpoint to Dr. Wang, I primarily see adults. So, it's not the general trend that somebody with the ADEM diagnosis would have a sort of gradual, insidious

worsening over time. So, my first response would just be to say that I wouldn't expect that. There's always an interplay between age and aging, which we see more often, of course, in adults in terms of the detriments associated with aging, if you will, and the disease.

[00:33:38] And so sometimes your body can compensate for a hitch to the nervous system, so, in this case, ADEM. And, you know, when you're young, your body can sort of mask some of the lesion's impact, but with age, because the nervous system does sort of naturally shrink a little bit with time, that's normal. Then sometimes I think of like the troops and all the like reserve function nervous system gets a little bit more used. And so then that just makes things like a gradual weakness a little bit more obvious.

[00:34:08] But my first thought is, you know, ADEM is really monophasic, even in adults and older adults. So, if there is gradual worsening, I think you really want to pay attention and see your physician and make sure that you're not missing something else. So, I don't consider it to be a slow, indolent process. I consider it to be a one-time, more acute process. So, I would just make that distinction for the person who asked it.

Krissy Dilger: [00:34:34] Okay, thank you. Dr. Wang, for patients experiencing brain fog or headaches, what treatments are available?

Dr. Cindy Wang: [00:34:41] Yeah, I mean, it's a great question. I think it's always good to kind of ask the person a few more questions. What do they mean by brain fog? Is it more memory? Is it more attention? When it comes to headaches, what type of headaches? Are they more tension headaches or some people have more features of migraines, which may affect only one half of the brain and be more kind of throbbing in nature.

[00:35:02] So I think really getting a better sense of the specific type of symptoms and what could be causing or at least exacerbating it, that would help, you know, with devising the treatments. When it is, you know, something as kind of vague as brain fog, I think having a neuropsychologist do formal testing so we can kind of break down and isolate, you know, that complaint into its individual parts can be helpful to propose specific interventions.

[00:35:28] And then headaches are so common in, you know, unfortunately you can get both ADEM and have headaches and they don't necessarily have to be related, but I generally do see patients who've had ADEM like Dr. Mateen's and maybe have a little bit lower cognitive or physical reserve that, you know, things that stressed the body may lead to more symptoms for those people than the typical person.

[00:35:51] But typically it's just, you know, what we use to treat those symptoms. So, headache preventative and headache abortive or rescue medicines are typically used. So, yeah, I think when it becomes that phase, when it's not the acute attack and there's not any concern for acute inflammation, we just treat things by the symptoms and, you know, kind of use the tools that we already have.

Krissy Dilger: [00:36:12] Okay, thank you. Our next question, is there any research or clinical trials currently being conducted on ADEM or anything related to ADEM, Dr. Mateen?

Dr. Farrah Mateen: [00:36:25] Yeah. And this is I think a really important point. So, I actually just went to clinicaltrials.gov, which is a publicly available website that you can look up any condition and see what's recruiting and what's reporting on in terms of clinical trials.

[00:36:40] And there really isn't any active sort of treatment trial recruiting right now. There are some registries and, quite honestly, I have some ideas and I know that there are some drugs that maybe could be repurposed, but I think this is where the association can really, and patients and people listening can really

be helpful in terms of advocating for more research and more efforts towards ADEM studies. You know, with rare diseases, we need collaborations across sites, and we need the partnerships of industry and people who are making the drugs.

[00:37:13] But right now it's not a full slate of trials or research going on. A lot of our work is retrospective, and it's honestly done with like unfunded graduate students or in spare time. So, we really need more sort of advocacy to get those trials going. But so, unfortunately, the answer is there's some things going on, not enough.

Krissy Dilger: [00:37:36] Okay, thank you. Our next question is about the COVID vaccine. So, are you recommending the COVID vaccine for your patients who have ADEM, Dr. Wang?

Dr. Cindy Wang: [00:37:46] Yeah. And, you know, I think everybody, you know, has their own thoughts about this topic. It can be a very touchy subject. I usually will, you know, inform my patient that, historically, the incidents of ADEM following, you know, like say a measles infection is much higher than getting the measles vaccine. So, you know, when we consider the level of stimulation to the immune system, typically infections will stimulate a vigorous immune response. So, and I think it depends on other factors. Like right now, we're in a time in the country in the world where COVID is very common, it's being, you know, I think spread. We're seeing dangerous variants.

[00:38:25] So, you know, usually I will make a recommendation for people to get it. And if they have specific concerns, if they say bring up, you know, my child has, you know, always had a fever, you know, their ADEM came very quickly after this. I might have, you know, a more nuanced opinion. In those cases, I would say at least, you know, every other family member who can get vaccinated, please do, and then certainly follow all the hygiene and the social distancing guidelines.

[00:38:54] But yeah, I think it's a nuanced topic, but there's definitely been studies. And I think one of the listeners' questions gets to, you know, the, are there specific vaccines that can lead to specific autoimmune illnesses with COVID? I see a lot more reports of COVID associated ADEM, COVID infection associated ADEM, rather more than, you know, COVID vaccine related infections.

[00:39:18] And I think we also live in a time where so many people are getting this vaccine at once. It's often easy to attribute if A precedes B, then A must cause B, and that's not always the case, you know, like 60, 70% of our country just got this vaccine within the past year or so. So, there's just naturally going to be instances of this condition happening and it can be true, true and unrelated.

Krissy Dilger: [00:39:42] Okay, great. Thank you. Dr. Mateen, I just wanted to throw it over to you and see if you have anything to add or elaborate on with that?

Dr. Farrah Mateen: [00:39:51] Yeah, no, that was a great, great discussion. I would say that I have followed several patients with ADEM, and they've all been vaccinated against COVID, and they've all done well. There's been no recurrence of ADEM or any other symptoms. So, the experience has been very good. And as you know, the vaccines that are created this time are the, for the most part, mRNA vaccines. It's a novel way to make a vaccine and it turns out to be highly successful against COVID.

[00:40:17] But we've had really good experience with the COVID vaccine in our ADEM patients and in our MS and NMO patients. So, I actually have no hesitation to recommend the vaccine in any of my patients so far. So, hopefully that helps people who are kind of on the fence. I think that the novelty of the way the mechanism of designing that vaccine makes it, you know, I think even more reassuring.

Krissy Dilger: [00:40:41] Okay. Thank you both so much for that. I know it's a question that a lot of people in our community have questions about and it's important. So, I really appreciate your input. The next question comes from the community as well. Are there any risk factors people with ADEM should be aware of in terms of developing further medical complications or issues or being at higher risk for infection, Dr. Wang?

Dr. Cindy Wang: [00:41:06] Yeah, generally not. You know, for other conditions sometimes we've seen like, in cases of people who have neuromyelitis optica go on to have other autoimmune diseases. For the most part, I've not seen that with ADEM I think it comes from our theory that it's just sort of a really unlucky instance of the right or wrong person, depending on how you look at it, encounters, you know, a specific thing at the specific time.

[00:41:30] So it's very unlikely, you know, that lightning would strike again. But I would say it depends on the amount of recovery. So, if there are significant motor deficits, then maybe, you know, it would be important to consider, you know, those in thinking about if there could be complications of illnesses or surgeries and so forth.

[00:41:50] So but, yeah, if a person recovers to near baseline, I don't really generally counsel that, you know, anything specific needs to be watched for. I generally recommend my patients just take vitamin D because so many people are deficient and usually you can't get into too much trouble just with the, you know, a moderate dose of vitamin D.

[00:42:11] But yeah, I think that is still extrapolating from other diseases such as MS. So, yeah, I don't think any avoidance specifically of any sort of, you know, situations or travel or any of those things is that necessary.

Krissy Dilger: [00:42:25] Okay, thank you. Our next question is, is there anything that can be done to help with nerve damage repair to help with lingering issues, Dr. Mateen?

Dr. Farrah Mateen: [00:42:37] Yes. That's a really hot topic in terms of, like, remyelinating the nervous system. The honest answer is the body's doing the hard work itself and there are medications that are being studied. I consider them like early phase trials right now. They're being studied more in multiple sclerosis or in optic neuritis because those are more common conditions.

[00:43:00] And they're, for that reason, they're a model that can be studied a little bit faster. But they're not primetime yet. So, there've been some trials that have looked promising, but then ultimately not succeeded. And there are some trials that are ongoing. So, I think this is a really exciting area. It's going to succeed at some point, but right now there's not one drug, one supplement.

[00:43:22] I would just caution folks not to spend their personal money on a bunch of like sort of supplements and other things that could be really expensive, but don't have evidence. So, just to be really honest with folks, there isn't really a over the counter thing you can take to remyelinate or to repair. It's really natural recovery until the science gets better.

Krissy Dilger: [00:43:46] Okay, thank you. We also got a question about pain. So, for someone who might experience neuropathic pain following an ADEM diagnosis, what are some treatment strategies for them, Dr. Wang?

Dr. Cindy Wang: [00:43:59] Yeah, if it's, you know, pain in general, I like to sometimes break it down in the parts. And if, even if somebody were to say neuropathic pain, I try to pin them on, you know, what type of pain is it? Where is it? What are the patterns that it happens? Just to get a better idea of where that pain might

originate from. Nerve pain or neuropathic pain tends to be more of kind of tingling pins and needles, burning, shock-like feelings. But there also can be other types of pain, such as, like, muscle spasms or stiffness, that would be treated with different types of therapies and medications.

[00:44:31] So, yeah, I think identifying the origin of the pain, is it even pain related to nerve damage. Maybe pain because you're weak in certain muscles and then you're putting, you know, undo or extra stress to other muscle groups or joints that weren't used to getting that amount of load.

[00:44:47] So, yeah, I think it really does depend on, you know, what the origin of the pain is. And then there are just general things that are good for health, like getting enough sleep, eating a diet that is nutrient rich, in terms of kind of just increasing and improving our everyday reserve of our neurological function. So, yeah, if there is a way to target a type of medicine or therapy, there can be specific classes of medicines for neuropathic versus, like, more specificity-related pain.

[00:45:16] And, you know, things to just supplement that would be lifestyle changes that could help. I think there have been other studies and different types of electrical stimulation. I think the group out of Hopkins had done some work on scrambler technology, but, you know, I'm not very privy to understanding what that is.

[00:45:33] So, yeah, I think there are definitely a lot of research and interest in approaches to kind of, you know, not necessarily rewire, but just kind of change the way your body interprets these signals. Sometimes when your body doesn't know what the signal is, I think the default is to interpret it as something uncomfortable. Yeah, so I think a lot of our interventions are targeted at just kind of decreasing the noise or the signal itself.

Krissy Dilger: [00:45:57] Okay thank you. We did also get another question from the community about lesions. So, can lesions actually heal over time or disappear? And if they do not disappear, do those lesions cause any kind of long-term outcomes for patients, Dr. Mateen?

Dr. Farrah Mateen: [00:46:16] Yeah. So, I guess the answer is that the lesions change, it's almost like a bruise in the brain. It's like originally, it's very inflammatory and kind of an angry lesion. It's got a lot of water and white cells and it's kind of attacking. And over time, the amount of, like, swelling and some of those angry cells end up moving on and there can be, they're no longer part of the picture, but sometimes the damage is done to the brain cells themselves.

[00:46:45] And so, it's kind of like a bruise that evolves over time. It might turn into a scar. In some cases, the body can very slowly, talking about months or years, repair and start to resorb some of that initial damage. And, in some cases, you know, people may not have ever had a symptom from it, but usually the amount of the impact of the lesion isn't high enough that it's going to be a really slow effort, in terms of the body trying to repair back to where it was.

[00:47:14] The lesions don't get bigger over time, but also, they usually tend to just kind of get a little bit smaller. They change their character on MRI. Sometimes, for example, if it's in a specific place that causes symptoms like, let's say, it's in the spinal cord, it may have had an impact on balance or walking, and maybe that impact will reduce with time.

[00:47:34] Either the lesion gets a little bit smaller, the body learns to compensate and find other pathways around it, but there's not a lot that can be done other than the body gradually resorbing that tissue damage with time. And so, a lot of the prognosis of ADEM really depends on that initial presentation, how big was the lesion, where was the lesion, and that kind of thing. And that kind of determines how much work the body has to do to get better.

Krissy Dilger: [00:48:00] Okay, great. Thank you. I think that's a great explanation. Unfortunately, we are at the end of our time. We just really appreciate both of you for joining us today. I just want to give you an opportunity, if you have anything you want to add or just close out with, Dr. Wang?

Dr. Cindy Wang: [00:48:16] Yeah, thanks for the opportunity. Yeah. I would say that, yeah, there are very few, like, kind of interventional studies, but hopefully with the amount of information we're gaining about MOG associated conditions, that would be a subset of ADEM, that, you know, I would be hopeful that we would start to have trials to develop treatments, particularly if it turns out to be a condition that you know, can really relapse over time.

[00:48:44] And then, in terms of just kind of studies of the natural history, the recovery with ADEM, I know some of my colleagues, Dr. Greenberg, Dr. Harder, at our institution, are heading up a study called Pediatric Sonics. That kind of gets to, you know, in ADEM, a lot of times, the MRIs look better on our current scanning, you know, MRI technology.

[00:49:02] But they're kind of interested in probing it further in higher resolution MRIs. Can we actually see, you know, scars at a more microscopic level? And then can we also assess function by doing, you know, thorough neuropsychological assessments? So yeah, I think there are going to be increasing opportunities for the community to engage with their doctors and scientists to, you know, better answer questions about how we can improve outcomes in ADEM.

Krissy Dilger: [00:49:29] Okay, great. Thank you. And, Dr. Mateen, any final thoughts?

Dr. Farrah Mateen: [00:49:33] I agree with what was just said, I think that was fabulous. Just to describe sort of how things have evolved. And I was looking at a paper, you know, we had worked on even like five years ago and I think things are changing. Sometimes, it's not so obvious, but I think that stay tuned and we're really appreciative of people who are willing to dedicate time for research studies and participate because that's how we continue to learn more.

[00:49:58] But things are changing. Sometimes it feels a little bit slow, but things are moving in the right direction. There are a lot of new therapies in neuroimmunology, and they're being tested first on more common conditions. But I think repurposing of some of those medicines will occur in the next few years.

[00:50:13] And I think it's actually really exciting that some of those drugs exist and they might actually be helpful. So, maybe that's just a plug to see your friend, really, a neurologist, maybe once a year, every, you know, depending on how you're doing, sooner or later, just because the world is changing in terms of what we have to offer. So, even if you're feeling well, maybe we have something else up our sleeve that we didn't have a few years back.

Krissy Dilger: [00:50:38] Okay, great. Thank you both so much. We really appreciate it. Just as a reminder, this podcast was recorded and will be made available on SRNA's website following today. Also I just wanted to let everyone know our rare neuroimmune disorder symposium is coming up next weekend, October 8th through the 10th. It's going to be virtual, so you can attend from your own home. You can find more information on our website, wearesrna.org, if you'd like to attend. Thank you both so much. And I look forward to hopefully having more resources like this in the future.

Dr. Farrah Mateen: [00:51:13] Thank you.

Dr. Cindy Wang: [00:51:14] Thanks so much for having us.