

# Adult ADEM

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[00:00:00] **Krissy Dilger:** Hello and welcome to the "ADEM Academy" podcast series. This podcast is titled "Adult ADEM." My name is Krissy Dilger from SRNA, and I will co-moderate this podcast along with Peter Fontanez from the MOG project.

[00:00:06] **Peter Fontanez:** Thank you, Krissy. Hello, my name is Peter Fontanez. My daughter was diagnosed with ADEM in 2014 and MOGAD in 2016. I have been a member with the MOG project since 2018 and have worked side by side with the SRNA since then as well. Thank you for letting us co-moderate the ADEM Academy with you Krissy.

[00:00:32] **Krissy Dilger:** Thank you, Peter. SRNA and the MOG project are nonprofits focused on support education and research of rare neuroimmune disorders including ADEM and MOGAD. You can learn more about us on our websites at [wearesrna.org](http://wearesrna.org) and [mogproject.org](http://mogproject.org). For today's podcast, we are pleased to be joined by Dr. Farrah Mateen. 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.

[00:01:21] Dr. Mateen's clinical and research fellowship training was in neuroimmunology and neurological infections at the Johns Hopkins Hospital in 2012, 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 Summer Scholar, 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 countries of various income levels. She has published 200 academic manuscripts to advance neurological disease research and clinical care to date. Welcome and thank you for joining us today.

[00:02:29] **Dr. Farrah Mateen:** Thank you very much, my pleasure.

[00:02:32] **Peter Fontanez:** Hello Dr. Mateen, so to start off the podcast, we want to ask, what is ADEM?

[00:02:38] **Dr. Farrah Mateen:** Yeah. So, that's acute disseminated encephalomyelitis and so, just taking one letter at a time, acute obviously means really rapid onset or within hours or potentially even days, but really sudden. Disseminated is referring to the nervous system or the central nervous system. So, that means its spread usually within the brain and the brain tissue, but also can include the spinal cord and even the optic nerves, encephalon means brain and then, myelitis is spinal cord and so, ADEM is the abbreviation of what

we're seeing, and it tends to be a more prominent is the word often used clinically. It's obvious, it's not like you would ask whether you have ADEM or not, it would be something really noticeable that involves the central nervous system. There are certain criteria for ADEM, for example, in children, but not adult criteria for ADEM and I'm sure we'll get more into that.

[00:03:42] **Krissy Dilger:** Thank you. That's a great explanation. So, how do adults typically present with ADEM? What parts of the central nervous system does it affect and how do they translate to symptoms in other parts of the body?

[00:03:58] **Dr. Farrah Mateen:** So, ADEM most of the symptoms that come to presentation are from the brain itself and so, what may happen is it may be mistaken for even like a stroke because like you have a sudden onset of weakness or you have a sudden onset of - in this case you can have a seizure, which is an electrical event in the brain or you can have a sudden onset of speech or language changes and then, sometimes people have what we call encephalopathy, which is a clouding of your consciousness. So, people may not be fully alert and aware, they may not be behaviorally or cognitively themselves, but again, it's really sudden and it's within hours, not over the course of months or years.

[00:04:43] **Peter Fontanez:** Doctor, we know that ADEM tends to occur more in pediatric patients than adults and I know you touched on the criteria for it. How does ADEM present throughout the various stages of life such as children, tweens, teens, young adults, adults, and geriatric patients and what are some of the differences between them?

[00:04:55] **Dr. Farrah Mateen:** So, children, it's a rare disease. I think it's worth mentioning. We're talking about having very little epidemiology of this disease, it's probably one in a million approximately or maybe one in 500,000, but in children, that would be the lion's share of ADEM, maybe if I had to estimate 80 to 90% of all cases of ADEM happen in children. So, under 18 and ADEM that occurs in adults, a significant proportion occurs in young adults, but we do know that ADEM occurs throughout the entire lifespan, which is somewhat surprising. We don't really know what causes ADEM. There's been a lot of speculation, maybe there's an infectious trigger. Rarely people thought there is a vaccination trigger, but it's something to do with the immune system itself and we know in children, the immune system is still developing in many cases.

[00:05:55] In terms of presentation in the pediatric criteria, there is the criterion of encephalopathy, so that clouding of consciousness that's meant to be part of the diagnosis. In adults because there are no criteria, we really don't have one specific way to diagnose it or not. There's no blood-based biomarker exactly. We do know that some people have a MOG antibody, which I'm sure we'll talk about a little bit more, which is a specific antibody to one of the cells in the central nervous system, but we don't have any obvious biomarker. In theory on pathology which is how ADEM was first recognized. So, ADEM was first diagnosed in the early 1700s and it was really in the case of pox in Europe. So, what goes back, 300 years now, that ADEM was first described and that was really diagnosed based on autopsy because that's really what they had available to them and over time now we have, things like CT and then, MRI, now we're having blood-based biomarkers and hopefully the field keeps growing, but if you do look in theory at the brain, then you can see there's a difference between ADEM and MS based on where the inflammatory cells are.

[00:07:21] **Krissy Dilger:** Well, thank you so much. So, for older adults what does having ADEM mean for their aging, especially if their condition isn't stable?

[00:07:24] **Dr. Farrah Mateen:** So, ADEM has multiple ways it can present in my practice. So, I have an outpatient neuroimmunology practice and I see ADEM and sometimes at first, it's unclear if it's MS or not

and so, it takes a little bit of sleuthing and sometimes time to sort out whether ADEM is what we call a monophasic presentation. That's almost always the case. So, unlike MS, which tends to be a disease that evolves and has multiple relapses over time, ADEM is really thought to be a onetime event. So, there's this more significant fulminant autoimmune presentation, but after that, many patients will be stable and there has been some work on cognition and continuing attention span and things like that after ADEM, but for the most part ADEM is a onetime event. It's not that it will happen again and again.

[00:08:33] So, it really depends on what happened during that one-time event. Was there visual loss? Were there language problems? Were there trouble with walking or troubles with bowel or bladder? If those occurred, then it's a recovery question about how much better could that person get right after that initial event, and can they continue to get better? In ADEM we don't expect that that would ever happen again and so, that's how it distinguishes itself from MS, which is much more common and has over 20 disease modifying drugs on the market and all of our attention is focused on preventing relapses. In ADEM we're talking about rehabilitation recovery after that initial event.

[00:09:17] **Peter Fontanez:** So, with the recovery, the way it is, does a patient with ADEM - can it cause long term disability in the body such as abnormal gait or balance? I know you touched on it just a little cognitive. Is there any long term instability, especially with geriatric patients?

[00:09:33] **Dr. Farrah Mateen:** So, in some patients, we're talking about lesions that are more than - roughly more than two centimeters in diameter. So, in the brain, this is high real estate zone and any brain tissue that was damaged by the original inflammation and autoimmune presentation, all of those symptoms are possible. So, if somebody did have an original trouble with walking or language or any of the things you just mentioned, all of those are possible to remain. The hope is that the body gradually recovers over time and so, we don't really have a medicine to promote recovery, usually when ADEM at first occurs, we do try to give things to combat the autoimmune system. So, the steroids and some people may have receive other forms of immune treatment like IVIG or plasma exchange even, even some other immunosuppressive medicines, all of that is meant to be like a fire extinguisher in the acute phase, but not everyone gets fully better with what we have available. So, all the symptoms you just mentioned are certainly possible and they can linger for many months or years after the initial event.

[00:10:47] **Krissy Dilger:** Okay. Thank you. So, in terms of recovery, is there a comparison between adults and children? Is it more difficult for adults to recover than children or is it pretty much the same?

[00:11:01] **Dr. Farrah Mateen:** So, there's limited work on this. We did do one paper looking at children versus adults with three other academic medical centers as well as our own and the prognosis in children is usually a little better. That's often the case, the young immune system and the young nervous system can recover a little bit better. So, the gradual improvement tends to be - the pace is the same, but generally kids get a little bit back to their baseline a little more. Having said that there are papers not by our team, but by groups in Europe, particularly in the Netherlands where they've looked at young children with ADEM and their long-term school performance and their ability to concentrate and memory and that often is a little less perfect than the controls of the same age and so, we do know that when the brain has had this really serious event that it can take years for the brain to really recover.

[00:11:50] And even if somebody looks normal again, they may still have a little bit of difficulty with processing time and attention at least based on those relatively small studies. I should mention that adults with ADEM we don't really have those studies. So, Adult ADEM is like I mentioned rarer than pediatric ADEM, both of which are rare and we just have a small number of adults with ADEM and so, there haven't been large studies

of rehabilitation and recovery or outcomes in that group, in fact, when we published our Adult ADEM of approximately 220 cases that was one of the largest series out there because we just have so few people that are being tracked and followed over time.

[00:12:55] **Peter Fontanez:** Thank you for that. Doctor, I know you touched earlier about the likelihood of - the chance of relapse. If a patient does relapse - is it possible that a patient that can relapse with ADEM and if so, what is the likelihood of it happening and how-- will the presentations be different and do you guys also start considering other diagnosis such as MS, MOGAD and other things of that nature if they do relapse with ADEM?

[00:13:23] **Dr. Farrah Mateen:** It's a great question and it's a question we often get in the clinic, and this is one of the fields right on the frontier of understanding what is going on in the central nervous system. So, ADEM by definition is monophasic. It happens once and it's not meant to ever happen again and that is the true definition, there are very few cases and it's a controversial thing whether you can get relapse in ADEM and that's been reported in a few children. In adults, I would be highly skeptical of that diagnosis of relapsing ADEM. In children, it is technically possible, but extremely unlikely. When you start to have two events over time, usually to answer the question, they affect different parts of the central nervous system. So, it's the same general central nervous system attack, but it's not the same part of the brain. It's not the same symptoms, it would be different symptom the second time and if you get two attacks of the central nervous system, this is where it becomes more and more likely to be an evolving condition like MS and so, this is where you really need the neuroimmunology experts to look at the case by case details to make that really important distinction because as mentioned, MS has what we call disease modifying therapies that prevent future attacks and certainly you would never want a future attack.

[00:14:50] So, if it is MS, you want to be ahead of that and make sure you've got the medicine on board and there are people whose clinics are totally dedicated to sorting these really fine details out and since you're coming from the MOG project, there is an antibody called myelin oligodendrocyte glycoprotein or MOG and that antibody is found in some cases of ADEM. Not all of them, but certainly MOGAD is an evolving entity that's being recognized and we're still understanding with children and adults, with MOG, what's the normal disease course of ADEM. I should mention in my adult practice of ADEM, it's very unlikely to have a MOG antibody. So, I think MOG ADEM is very much a pediatric disease. The average age of onset is probably around seven or eight and in adults with ADEM, it's extraordinary to see a MOG antibody. I'm trying to think of a single case I've seen actually. So, it's not impossible, but not very likely either.

[00:15:58] **Krissy Dilger:** Thank you. So, how does an older or geriatric patient distinguish symptoms of a relapse of ADEM with aging symptoms? So, for example, forgetfulness, visual issues, mobility issues and those sorts of symptoms.

[00:16:18] **Dr. Farrah Mateen:** So, if a symptom comes on rapidly, neurologists really use time of course very carefully. So, if something's coming on suddenly or rapidly, we think of that as more of an acute or the A of ADEM thinking about that or for example, if you also have risk factors for other things, you have to just keep that in mind. Sometimes people have arthritis, or they may have risk factors for hypertension and stroke and so, it does depend on the time course and how things are evolving. If there's, gradual day to day changes, it's really good to ask your neurologist for a baseline assessment. So, for example, you had mentioned memory and thinking, you can do a baseline cognitive test and get your normal and figure out what that is and then, if you find that things are changing over time, that's where we can get in our allied health care workers and try to sort out if there is truly a measurable change and if there is, is that related to some of the things that have already been happening or are there new changes. So, that's where testing becomes very helpful and things that get worse gradually over the course of months or years, those tend not to be ADEM itself, those tend to be other things, potentially aging or other conditions.

[00:17:46] **Peter Fontanez:** Thank you. So, I know with pediatric ADEM, it affects children's cognitive and behavioral, and it could affect those aspects of a child. How does ADEM affect adults cognitive psychological or behaviorally and if so, what does it look like and how are patients to know that this is part of an illness as opposed to a generalized mental illness?

[00:18:09] **Dr. Farrah Mateen:** So, everybody's different. It's important to say that obvious statement that it depends on where your lesion is too. So, some people may have a lesion that is not really affecting their cognition or their memory or their behavior and other people may have that. So, it really depends on where ADEM has occurred and in many cases, we have people who will report anecdotally that they're just not as "sharp" or they may not remember as well, or they may feel more emotional. All of those things have been reported, but they're usually anecdotal. So, one person reporting it based on their experience. In terms of the whole group of people who've had Adult ADEM we don't have a cohort study or data. So, maybe for people out there listening, this is a study that needs to be done and we need to understand this better and it's worth doing. So, we can answer questions like you just asked otherwise we're going to be dependent on case-by-case reporting, but we do think as a field that there are potential deficits from having one catastrophic event in your brain and they may be subtle and they may be things that other people don't notice and just you as a patient may notice, but they can sometimes be detected on really detailed cognitive testing or for people who are doing complex tasks, they may find it takes them a little longer.

[00:19:48] In order to separate that from a new diagnosis, sometimes the testing, we also do follow up MRI there's no guidance on when that should be or how often that should be, but I can tell you in my practice if I've diagnosed, ADEM we think seriously about medication choices and we also think about when should we survey to make sure that this is not MS and that this is not - we're not missing something. We do check for MOG antibody twice. So, at the time of onset, but I will check it again six months afterwards, making sure we haven't overlooked an initial missed antibody and if you see that the MRI is stable or improving, which is almost always the case with the ADEM, then we have some reassurance that this is going to take time. If there's a concern about a different condition, that would often show up on an MRI too, but sometimes people with ADEM may feel under the weather, depressed, they went through a lot. Sometimes hospitalization itself can be depressing and it's a change in your life or your quality of life in some cases and so, it's important to tease out all those details.

[00:21:01] **Krissy Dilger:** Well, thank you for that detailed explanation. That's great. So, shifting gears a little bit, does ADEM cause bladder and bowel issues? Can patients expect to recover from these issues and if this is possible, what would the timeline be? Does it depend on therapy or what does it depend on?

[00:21:28] **Dr. Farrah Mateen:** So, bowel bladder issues really come from the spinal cord to the M of ADEM. So, all being said the spinal cord, if it is involved, it's not always involved in ADEM. So, in adults, we found that about 40% or so of patients had myelitis at the time of onset and those are the patients who would be more likely to have bowel and bladder changes and what those can involve are urgency so, having to go right away, hesitancy so, thinking you have to go, but not being able to actually go and then, also incontinent, so losing control or direction over having urination or bowel movement and so, all of those things are possible and those come from the spinal cord, which is really the control of the fecal and urinary output and the brain obviously oversees all of this, but the spinal cord is the executor of all of that and so, when the spinal cord is involved, it can get better and often it can get better quickly.

[00:22:38] For example, if somebody has steroids or an immediate treatment, you can start to see recovery within the first days, but then in some patients, there is lasting spinal cord impairment and the spinal cord is like also a high real estate zone, it's not a very big structure and if you have a lesion in it, then that really slows the signal from the brain down to the bladder and the bowels and so, in terms of recovery, we expect

most recovery to happen within the first months, maybe the first year if you'd want to stretch it out, but after that period of time, if you're not noticing a lot of recovery, then the recovery pace is really, really slow and it doesn't mean it doesn't happen, it's just a much more gradual process and we think some of that tissue is damaged and then, there are other workarounds that you can do with symptomatic medicines. Even things like Botox and the bladder and things that you can go to your urologist or GI doc for, but in terms of nervous system recovery, a lot of it is really early on

[00:23:44] **Peter Fontanez:** On a similar subject, does ADEM cause sexual dysfunction in adults? Is this recoverable? What kind of reproductive implications can this have for adults wanting to have children?

[00:23:55] **Dr. Farrah Mateen:** So, those are good questions. So, in terms of sexual dysfunction, it does tend to track with bowel and bladder dysfunction. So, a lot of folks who have bladder problems or neurogenic bladder, neurogenic bowel, there is also sometimes sexual dysfunction and that's because of the spinal cord and its important role in controlling those nerve signals and that has been less well studied, to be honest. So, there isn't a lot of work on this. There aren't really any reports that I'm aware of that have specifically looked at this, but it's certainly the case based on clinical experience that it's possible. In terms of reproductive potential, ADEM doesn't really affect fertility for men or women. So, it shouldn't affect the ability to conceive, but in terms of if there is a spinal cord presentation in a woman with ADEM, then we would work carefully with like a higher risk obstetrician to try and make sure there aren't any risks or at least that that person's properly followed, but there's really no known impact on fertility and we do use a lot of immunosuppressive medicines and some of those can have effects on fertility, but if that's something that is a possibility for a patient, then we'd want to hear about that so we can choose our medications accordingly.

[00:25:16] **Peter Fontanez:** Thank you. You touched earlier that a percent that some patients test positive for the MOG antibody with ADEM. Now you said that's more in pediatrics. What is the likelihood of an Adult ADEM patient having MOGAD and does this increase their likelihood of relapsing?

[00:25:35] **Dr. Farrah Mateen:** So, adulthood is hopefully a long time for people. So, between 18, all the way to, let's say 100, in young adulthood then MOG antibody is a little more common. It's a spectrum or continuum. So, if you're going to get MOG antibody as an adult, it's much more common in people in their late teens, 20s, maybe 30s, but I've yet to see - I'm trying to think of a case where I've seen MOG antibody and ADEM in somebody beyond that age range of 30 and above and it's really hard to think of a case. I've certainly seen a lot of ADEM in adults, but we don't have a lot of MOG positive. I would give you the caveat that MOG, ADEM is rare and that Adult ADEM is rare. So, let's say we only see a couple cases or a few cases a year as a referral center for Adult ADEM, particularly in like the 40 and above range and MOG antibody's only been available for testing for about four to five years approximately and the testing is now very good, but if we're only seeing a few cases and the antibodies has only been available for clinical testing for a few years, we really have small numbers to work with, but it's very rare to have a MOG antibody in Adult ADEM based on experience.

[00:27:01] But we don't have like the full. ADEM is not a reportable disease and so, we don't have like the national experience or even a statewide experience. It's really just based on a researcher, someone like me going back and looking at records with our graduate students, our fellows who - well, there isn't really a lot of funding to do ADEM research overall. So, a lot of this is voluntary work that gets done by people on training or people who have a professional interest, but there isn't a registry that's really like to my knowledge, at least looking at this. In terms of risk or relapse from a MOG antibody, in theory, a risk of relapse of something in the nervous system with a circulating MOG antibody is probably a little higher, but hard to quantitate that. That's when people would start thinking about should we be giving an immunosuppressive therapy for MOG? That remains controversial, but I think if you did have the MOG antibody in your blood, then it would certainly be a question worth discussing with your neurologist.



[00:28:12] **Krissy Dilger:** Thank you. So, just a few questions and the next few questions will be about testing so, what testing is used to diagnose a patient with ADEM?

[00:28:25] **Dr. Farrah Mateen:** The most important - in neurology, the most important besides the history and the exam it's the imaging and that's because we really can't get biopsy of the brain in most cases. Well, we wouldn't want to do that unless we absolutely had to, but this story, I mentioned a lot about time course and symptoms, and this can be challenging in children who may not report some of their symptoms. We did look at this in terms of what kids versus adults report. Kids sometimes have more like what we call ataxia or imbalance. They're less likely to report sensory symptoms and they're more likely to have that encephalopathy, which is the more classic consciousness change, they're more likely to have seizures because the lesion is taking up a part of the brain and changing the architecture of the brain. So, that's worth noting and then, what was the end of the question again? Sorry.

[00:29:28] **Krissy Dilger:** I think that was just what testing is used to diagnose the patient with ADEM.

[00:29:34] **Dr. Farrah Mateen:** Yeah. So, the MRI is our gold standard and then, we do the MOG antibody it's usually in the blood and sometimes people will do the cerebral spinal fluid test. So, some patients have had a lumbar puncture. A lumbar puncture is a needle that looks at the fluid that bathes the brain and spinal cord and it's a safe test, but it's irritating to have a needle in the lower back and most of the time that's to rule out other things. So, it's really to make sure there's no infection causing ADEM or no other mimicking diagnosis. So, it's not really proving its ADEM, its ruling out other things. Sometimes there is an eye exam if it's possible where you can look at the back of the eye and that's because the optic nerve is embryologically the same as the brain and the spinal cord. So, you can see the very tip of the optic nerve if you do a good eye exam and so, sometimes patients will have optical coherence tomography or OCT, which is a little picture of the back of the eye, but the majority of cases are diagnosed purely based on brain and spinal cord MRI and as I mentioned that there is a group of patients who have had a biopsy of the brain and that's because the diagnosis wasn't clear and they wanted to understand, is this something like ADEM or is this a lymphoma or tumor or other things or infection? So, sometimes ADEM does get diagnosed by biopsy because of the complicated way in which patients present.

[00:31:15] **Krissy Dilger:** Thank you and you mentioned that the MRI is like the gold standard and imaging is really important. So, I guess for the like people listening, is there anything you can describe about the typical presentation of ADEM on an MRI? Like what you look for when you're reviewing those imaging?

[00:31:38] **Dr. Farrah Mateen:** Yeah. So, the most important thing is looking at the size of the lesion for me. So, a lesion that's roughly more than two centimeters in diameter and that's really the fulminant characteristic of ADEM and there are also like where the lesion itself is placed. We know that in certain cases it can be in certain parts of the brain. So, the frontal lobe, there's also some work about ADEM being involved with what they call the deep gray matter of the brain. So, it's like the thalamus, which is a sensory relay station. So, there's some parts of the brain that are more likely in ADEM, but what we're really looking for is a really like large white matter change in the brain plus or minus spinal cord involvement and that's really the beginning at that disseminated and sometimes it's a solitary big lesion and sometimes it's a few big lesions or a big lesion, a few medium size lesions. Sometimes it's a big lesion with the spinal cord involvement. So, it doesn't have one exact pattern, but we're looking for that. In this case the D, like the bigger lesion and then, the A, which is acute, which means sometimes there's like swelling around that lesion or edema because it's actually quite sudden.

[00:33:00] **Peter Fontanez:** Thank you for that. Now, with some patients in the community have stated that they've - for other demyelinating conditions, they stated that they've had MRIs not finding lesions upon

onset of symptoms and then, later on a second, MRI being done several weeks later and finding now lesion activity. So, the symptoms preceded the MRI findings. Can adult patients with ADEM have symptoms before the findings on the MRI present itself?

[00:33:27] **Dr. Farrah Mateen:** I think yes, you can definitely have symptoms that crept in or that they may have been subtle. Maybe the lesion wasn't so big at the beginning and then, all of a sudden it became to the point where it was noticeable. So, in retrospect, some people will say, "Oh, yeah, my symptoms started in a much smaller fashion or a much milder, barely noticeable fashion some days before, but it wasn't of the like magnitude that brought them in." Usually MRI changes, they don't happen within seconds. They do take some time to evolve, but it's generally the case that the symptoms bring people in and then, the imaging confirms the symptoms. It's less likely that the symptoms just gradually crescendo. If you play music that they crescendo over weeks, usually they're subtle and then, poof something happens.

[00:34:23] I'm trying to think of other important factors. In children, especially there is this preceding event or antecedent event that's been very well recognized in the literature in terms of infections and in terms of occasionally vaccination. So, if there is a really bad infection that - or even a mild infection within the last month or six weeks or so, then sometimes in retrospect, that preceded the ADEMs that may have been like a viral trigger and it's not one virus or one bacterium or one vaccine, it's just something about the immune system may have been triggered in those cases.

[00:35:17] **Krissy Dilger:** Thank you. So, is there a way to rule out other types of demyelinating conditions such as, TM, NMO, MOG antibody disease while you're doing those initial tests?

[00:35:36] **Dr. Farrah Mateen:** To rule out -can you give me the list one more time?

[00:35:43] **Krissy Dilger:** So, just like while they're getting those first diagnostics, how do you rule out other types of demyelinating conditions like transverse myelitis, NMOSD, acute flaccid myelitis, all of those?

[00:36:00] **Dr. Farrah Mateen:** So, I think that it's really important to think through what you're trying to rule out and why. So, in some cases, it may be that you're trying to rule out things that have a specific bio marker and I'm trying to think of - for example, like aquaporin-4 antibody, NMO, we do have a blood test that's sensitive and specific for the diagnosis and therefore, we would really want to rule all that out and that's important that we can do that. The other diagnoses sometimes can be more difficult to rule out and so, they may be pattern recognition and it may take time to be 100% confident. MS being an example, there's no one blood test for MS and so, your doctor may initially say, I really think it's ADEM, I'm very confident, but it's still important to watch this and then, there may be certain infections that are worth checking or certain, like I mentioned lymphoma that may sometimes mimic ADEM or lupus, which is an autoimmune condition. Some of those do have some tests that can be done either in the spinal fluid or in the blood or just in general, for example, urine analysis, some of those things can be done to effectively rule out those diagnoses, but it does take - it does sometimes take time and it really depends on each person's presentation. Like if you have more of a brain presentation, then you may be looking at specific things. If spinal cord is involved, you may be looking at other things.

[00:37:35] **Peter Fontanez:** Thank you for that. We're going to go ahead and move on to treatments now, what treatments are available for adults having an active ADEM attack?

[00:37:46] **Dr. Farrah Mateen:** That is based on many years of anecdotal experience. There's never been a randomized controlled trial, but it's really somewhat borrowed from the MS literature, and it makes good sense that IV steroids are really the treatment of choice for acute ADEM and the duration of those and the



dose of those are not standard, but often people get a gram a day for three, five days, sometimes longer. Sometimes people will get an oral pill or steroid taper and some people won't. So, there's not like consensus on that. If patients continue to not do well or not show recovery, then we start thinking about other forms of acute immunosuppressive therapy. So, for example, we may think about IVIG or intravenous immunoglobulin, which is basically a pool of blood product to try and flush I guess the bloodstream of an antibody that could be causing ADEM and in some cases, there's plasma exchange, it's used, which is taking out your plasma, which is the part of your blood and filtering it and then, putting plasma back into you and that goes through a certain line in the vein and that gets often done every other day.

[00:39:15] In children, many pediatricians don't treat to the ADEM at all. They don't, maybe rightly so that they don't think that there's any evidence to treat and people can recover either way. In adults, we often use steroids as a first line, but again, no exact randomized trial. So, there's not one right answer and there's not one wrong answer. Sometimes we've done research on this. So, we published this in a couple of different journals that patients will sometimes get MS type of drug or sometimes they'll get rituximab, which is a B cell therapy, which tends to deplete a certain lymphocyte or certain immune cell, which is thought to be involved in ADEM and that is a long lasting IV medicine. We've used that certainly in several of our cases and it probably does help with inflammation and it helps prevent any future, I guess future attacks or future flares of the disease, but again, controversial, not necessarily based on a high level of evidence, but a variety of things are done to try and temper the immune system and to try and get that fire if you will, smothered.

[00:40:34] **Krissy Dilger:** Thanks. So, for those acute treatments that you just listed, would those be the same treatments used for a relapse then?

[00:40:46] **Dr. Farrah Mateen:** With the caveat that if you're getting a relapse in ADEM it may not be ADEM and so, that's really when you want to get a neuroimmunologist just involved with your care and if it's a relapse, then that changes the thinking about what the diagnosis is in many cases and if the original treatment plan was the right one.

[00:41:09] **Peter Fontanez:** We're going to move on to long term care now. What can adult patients with ADEM expect with the recovery and how long can it be expected to take?

[00:41:20] **Dr. Farrah Mateen:** In many cases, recovery happens very early and that the most recovery happens really in the first days and weeks and after that, the recovery can be really slow. So, most recovery and neurological diseases happens in the first six months, approximately maybe up to a year, but we're expecting most recovery in the early days and early phase of the disease. Having said all of that there are people who continue to show gradual improvements over time and there are also things that people do to make sure that their recovery continues. So, being physically active to the extent possible and stretching and exercising and making sure they're doing the most they can to strengthen their contra-lateral muscles and to make sure that they're preventing other co-morbidities. So, they often say use it or lose it. So, we do subscribe to that in neurology that we want people to continue to maintain active lives and to continue to use all the best functioning that they can in order to preserve their nervous system and their muscles and all the things that they can do day to day.

[00:42:40] **Krissy Dilger:** Thank you. For patients who have had physical bladder and bowel and sexual dysfunction problems with ADEM, what are some of the options for therapies for gaining some or all functionality back?

[00:42:55] **Dr. Farrah Mateen:** So, there are entire fields dedicated to urology and GI and sexual dysfunction. So, those are each should be taken somewhat separately, and we would work with our colleagues in each of those fields to try - for example, in urology, gynecology, GI to try and make sure we're using the most up

to date science and also in physical medicine and rehabilitation are also called physiatry. Those tend to be colleagues that are extremely helpful because they have thought a lot about spinal cord across disorders. So, we think about it, I'm a neuroimmunologist. I'm thinking about a lot of the medications and the acute treatment, but there is a whole field of rehabilitation and recovery and if you haven't seen a doctor of that specialty, that's really often worth your time because they have other - I want to say tricks up their sleeve and other knowledge bases, which is their whole career.

[00:43:55] And for example, in terms of bladder, we've learned a lot about bladder from other forms of spinal cord injury. For example, traumatic spinal cord injury and they have things that they can do like Botox or medication management with urology and it's really important for - we've been talking about older adults. When you have a bladder problem, sometimes ADEM is 100% of the cause, but sometimes it's 10% of the cause or 50% of the cause and there may be other things to think about like prostate or urinary tract infections and those things can be addressed as well and even if the ADEM cannot be fully addressed, some of those things creeping in a little bit can all be addressed and then, you can go back to a very comfortable baseline by treating the easily or more treatable things, but there are a variety of medications depending on the type of problem. So, if it's urgency, there are certain medications, if it's hesitancy, there are other approaches if there's incontinence or other things to think about. So, it depends on what exactly the problem is. There's a whole list of medications and options for each of those.

[00:45:12] **Peter Fontanez:** We know ADEM can affect the cognitive and behavioral functions. Should a patient follow up with a neuropsychologist?

[00:45:21] **Dr. Farrah Mateen:** If that's something that affects you, if there's cognitive or behavioral changes, then a neuropsychologist can be really great at articulating what the problem is. So, sometimes people know that there's a problem, but it's hard to tell exactly what the problem is. Is it attention, is it memory, is it just complex interactions or executive functioning? So, a neuropsychologist can help tease out what the source of the problem is. Sometimes if you're not paying attention, you can't remember that's different than a primary memory problem and so, it's really helpful for people to know what's going on and then, after that, neuropsychologists are really helpful at strategies or cues or other ways for people to mitigate or to combat what's going on.

[00:46:15] And sometimes we share our patients with neuropsychiatrists or psychiatrists or psychologists who can help provide either cognitive behavioral therapies or other strategies or even medicines if there are behavioral changes or cognitive changes. We don't have a great memory pill for example, but if people do find that they're having a low mood or if they're having some difficulty with their behavior, we do have some medicines for that or fatigue, which we haven't talked about yet, which is very common in people who've had neuroimmunological conditions. We do have medicines for fatigue and none of them are what we call on labels. So, the USFD has never approved any of these medicines specifically for ADEM because it's really rare, but we do borrow those from other conditions, even MS and multiple other conditions.

[00:47:12] **Krissy Dilger:** And what advice or precautions can you give a geriatric patient with relapsing ADEM who is living alone?

[00:47:23] **Dr. Farrah Mateen:** I think the first would be to make sure you really have relapsing ADEM because I think that like I mentioned is really rare and I guess I'm a little bit curious if that's exactly the right diagnosis or not, but presuming it is, I think having a strategy for the things that are the result of the ADEM and so, in this case, I'm not sure exactly what the symptoms were, but if you know that you have difficulty with mobility

or falls and have a button or have someone checking on you once a day or if it's memory to have, sometimes they are like electronic solutions where you can have pill bottle reminders or you can have other things that can help you remember what to do. If there are other issues like - I'm trying to think - I'm trying to guess what this particular case was, but in terms of like language and you can work with speech language.

[00:48:28] But, I think it's really good to just have a network, have a new immunology expert working with you because there aren't lots of people with this to like connect you. I think, obviously these foundations that are part of this podcast may have additional resources and ideas and put people in contact with other patients or other experts. So, I think you're probably best to promote your own work, but I know that patient foundations are really good advocates and resources for patients to especially for rare diseases because they're not going to be 100 people in a neighborhood to discuss this and if you talk to your friends or neighbors, they're not going to know what this is and so, I think that just educating people around you using some of those resources would be really helpful.

[00:49:18] **Peter Fontanez:** Thank you. We're going to move on to a few community questions real quick. I know you touched earlier on the likelihood of relapse, a patient with ADEM who is in their 60s said that when they push themselves physically beyond their normal, they tend to trigger a relapse of ADEM. Can a patient trigger an attack through overexertion or is this something more like possibly Uhthoff's or something of that type?

[00:49:47] **Dr. Farrah Mateen:** It's a good question. It's highly unlikely you're actually creating an attack. So, that's true across all neurological disorders. You can't just will on an attack or stress as bad as it is, doesn't usually create a new neurological or new neuroimmunological event. So, it's highly unlikely that you can will on or even like due to ambient circumstances, create an attack. So, I'd say that's less likely. The flare or the pseudo flare, the worsening of prior symptoms, that is possible. When people are under like stress or heat or exhaustion or those sorts of circumstances, you can certainly get worsening of your prior symptoms and that's not unheard of at all and that may not be damaging to the nervous system. It may just feel really miserable to have all those old symptoms come back. Whether those should be treated with a medicine like steroids is something that you'd want to talk to your neurologist about whether a flare really is something you'd want to take immune-suppression for or not, or whether you can try to your best possible way to try and get rid of some of those stressors, but it's not likely that you can just create a relapse.

[00:51:24] **Krissy Dilger:** Thank you. We did get a question about vaccines. So, what is the relationship if any between ADEM and vaccines?

[00:51:38] **Dr. Farrah Mateen:** So, most people have no relationship between vaccines and ADEM, but there are cases and they're legitimate of usually children of a vaccine that for some reason is associated in that particular case with ADEM and those are few and far between and they may be related to - excuse me, host factors by that, we mean the person more so than the vaccine itself and it may be that that person was very susceptible already, but this is really a - first of all, it's controversial, but it's also really unlikely. It's really rare, but there are cases reported that vaccine has been triggering to a case of ADEM and it is something that the CDC has worked on for decades now to try and have a reporting system and try to understand if there are specific vaccines or specific ages and there is a much larger literature and program on this about basically the CDC will cover somebody who's had ADEM from a vaccine, but in general, it's a tiny, tiny, tiny group of people with ADEM and it's not one vaccine and it's not one age group and there have been several reports. For example, the rabies vaccine has been reported to cause ADEM we even did some work on COVID vaccine and ADEM, but we're talking about one in many, many, many million and so, even if you've had ADEM in the past, that doesn't prevent you from getting a future vaccine because we think that that isn't a recurring process.

[00:53:24] **Krissy Dilger:** Thank you. So, we had another question from a listener. What types of medicines or supplements were you referring to in regard to fatigue?

[00:53:38] **Dr. Farrah Mateen:** Well, the whole fatigue literature is a little murky just to be honest, but there are medicines that we borrow from like the MS literature. In terms of supplements, there's no definite supplement that works. Some people have tried coenzyme Q10 which is an over-the-counter supplement, and it may or may not work, but it might be worth a try if somebody has fatigue because it's inexpensive and available and if it works great, there is some literature in MS as mentioned and that literature is mostly positive, but it's in small numbers so we couldn't say for sure that it works. There are medicines that are approved not for fatigue and AEDM or even fatigue and MS that list would include Provigil or Nuvigil. Those are more stimulating medicines. Those are prescription only and those are really on the market for things like narcolepsy, but we know that they can work in a lot of patients with a fatigue from neuroimmunological conditions. That's something you'd need a prescriber and it's scheduled in the sense that you have to have a refill like every 60 or 90 days, depending on where you are.

[00:55:00] There are medicines like Ritalin has been tried. There are other stimulants that have been tried that are on the market for ADHD and those can work as well, but they should be taken judiciously and those are more if you take it, it works and if you don't take it, it doesn't work. There's a medicine called amantadine which is a pill. It's on the market for fatigue and it's really also a flu preventative and it was tested. Amantadine is old medicine. It's a pill. It was tested in Parkinson's, it was tested in traumatic brain injuries, tested in cancer fatigue and it tends to work, but it's a mild or daily agent and some people find that that's helpful as well because it's just a gentler approach to fatigue. So, that would be my short list, there's always things changing and the other thing that's worth mentioning is some people have apnea. By that, I mean, they're not oxygenating well, when they're sleeping sometimes because people have ADEM with a lesion that may change the way that they're breathing really, other people may have like thyroid conditions or other reasons why they're fatigued anemia. So, it's really important for people to go to their doctor and explain that they're fatigued and so, that can be sorted out. Is it fatigue from ADEM or is it fatigue from something else? That's the first decision.

[00:56:34] **Peter Fontanez:** Thank you for all that. We just have one last question for you, Doctor. We wanted to ask you, is there any current studies you're working on with ADEM or anything that you're working on for any demyelinating conditions and if so, what can the community do to help you?

[00:56:51] **Dr. Farrah Mateen:** There's a lot of work that I would like to do. I've been doing some work on ADEM versus MS, which is one of - I think the one of the most important questions for patients. Is this a lifelong recurring condition or is this a onetime condition and also as an adult neurologist interested ADEM we're trying to do some of the work that we've just mentioned about what are the long-term impacts of ADEM and what if we didn't give a B cell therapy like rituximab or ocrelizumab or some of the other -mabs out there? Maybe some people on the podcast are on these medicines, but we don't have good outcomes data. So, all of that really needs to be synthesized as a larger group so that we don't keep guessing patient by patient on what the right thing is. We have our good strong expertise and impressions, but what we really need is robust data where we can collaborate across centers and so, I mean, the reality is we really need more funding towards ADEM and Adult ADEM in particular.

[00:57:54] And we need to be able to have that funding to create some of these registries and to bring people back in and reassess them for some of the things we mentioned like cognition and mood and to create a database and then, for future patients answer the questions that exist particularly in adults. Children, I think the pediatricians are getting much more organized, they have consortia. Adult ADEM hasn't had the same attention and so, patients are left with even fewer answers, and they may get answers based on the

pediatric literature, that's not really fair to them. So, I think we really just need more funding to even start to work together to answer these questions because a lot of these are projects done by really dedicated like graduate students or fellows who find it really important, but that's not sustainable over time. That's only, a year or two and then, they have to move on to other fields because they haven't got funding to keep going. So, I think to have sustainability is really important.

[00:59:03] **Krissy Dilger:** That's such a great point and thank you for answering that for us. Unfortunately, we've reached the end of our time. We are so grateful that you are able to join us today and answer these questions. I know the community, both the MOG project community and the SRNA community really appreciate you taking the time and answering our questions, so hopefully we can continue this conversation in the future.

[00:59:31] **Dr. Farrah Mateen:** Yeah, my pleasure and thanks for all the work you're doing and really my privilege to be on the podcast.

[00:59:37] **Krissy Dilger:** Thank you.

[00:59:38] **Peter Fontanez:** Thank you. Thank you for having us.